

SUPPLEMENTAL FIGURES

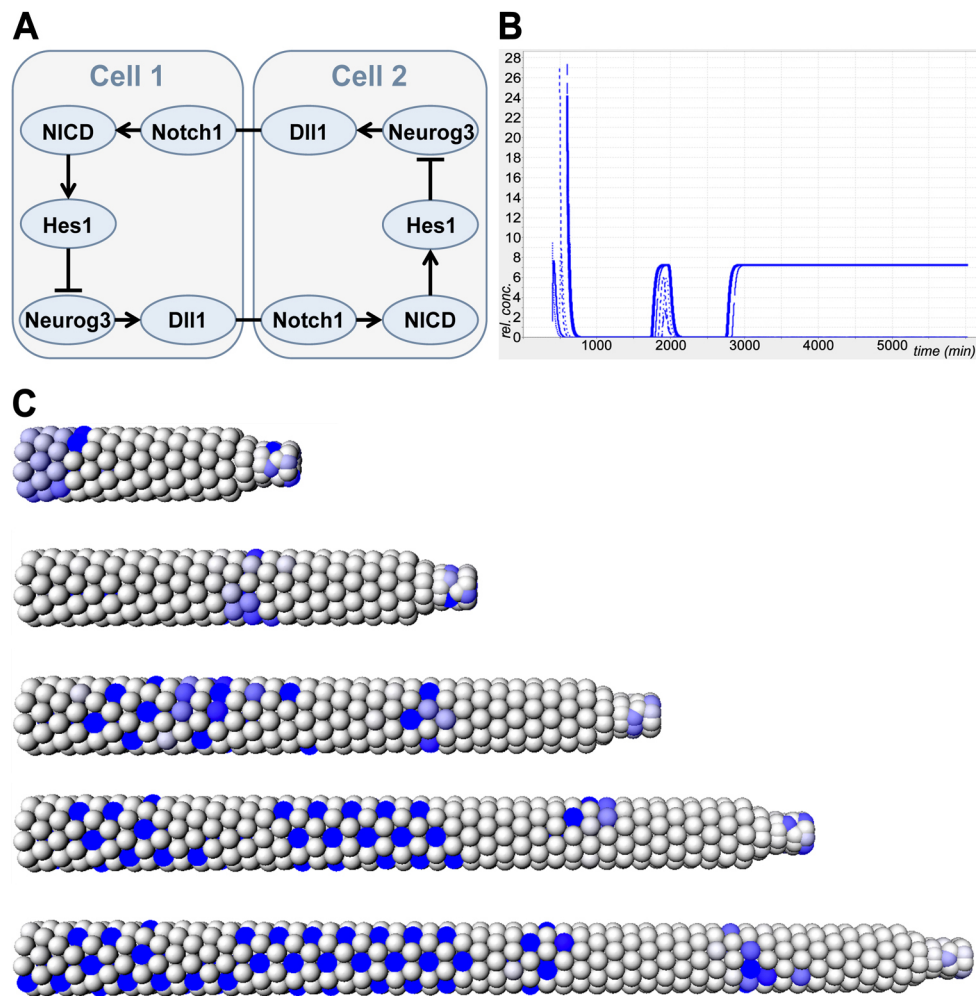


Figure S1. Simulation result with initial noise. Shown are results for a GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3*. Initial noise is added to all concentrations of newborn cells but not introduced by transcription stop during mitosis. (a) Reaction scheme for two neighboring cells. (b) Time course of *Neurog3* mRNA expression in a ring of nine cells. (c) Snapshots of the simulation show *Neurog3* mRNA concentration as blue color intensity for each cell. Time points chosen are 1500, 2500, 3500, 4500, and 5500 minutes.

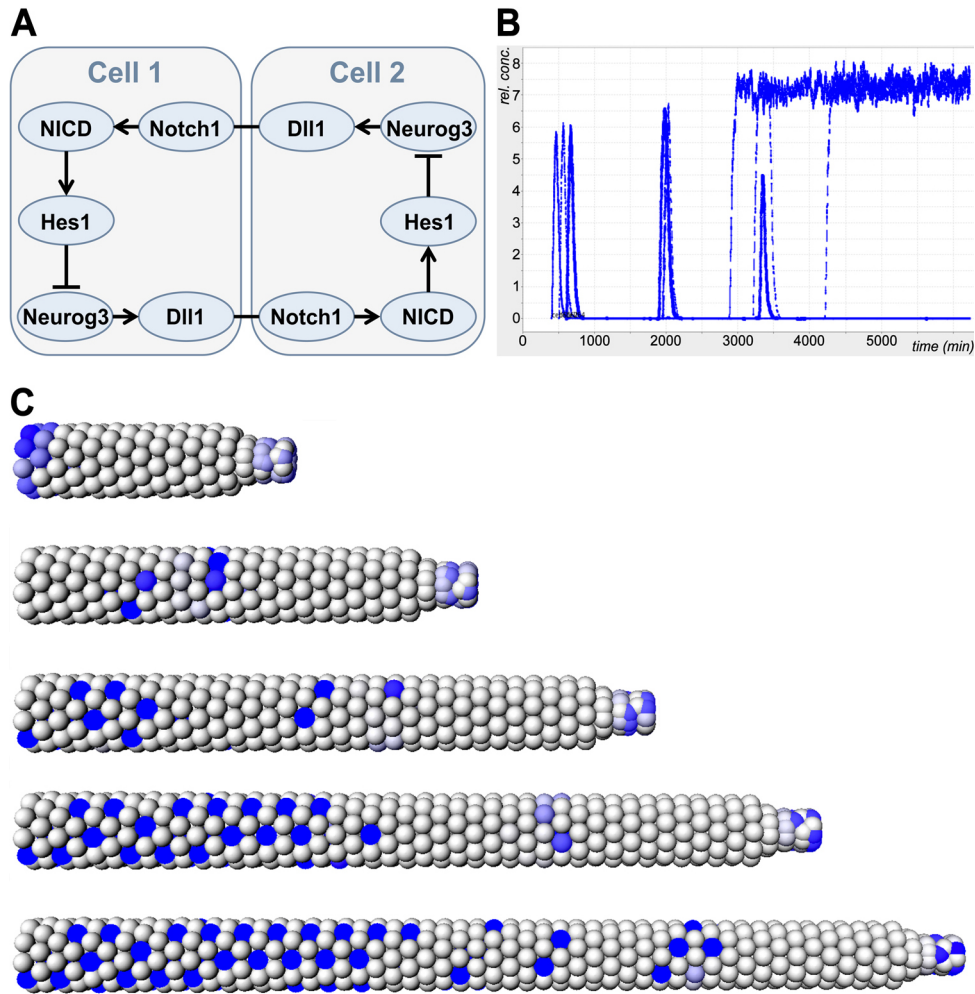


Figure S2. Simulation result with stochastic noise. Shown are results for a GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3*. Noise is introduced by chemical Langevin equations. (a) Reaction scheme for two neighboring cells. (b) Time course of *Neurog3* mRNA expression in a ring of nine cells. (c) Snapshots of the simulation show *Neurog3* mRNA concentration as blue color intensity for each cell. Time points chosen are 1500, 2500, 3500, 4500, and 5500 minutes.

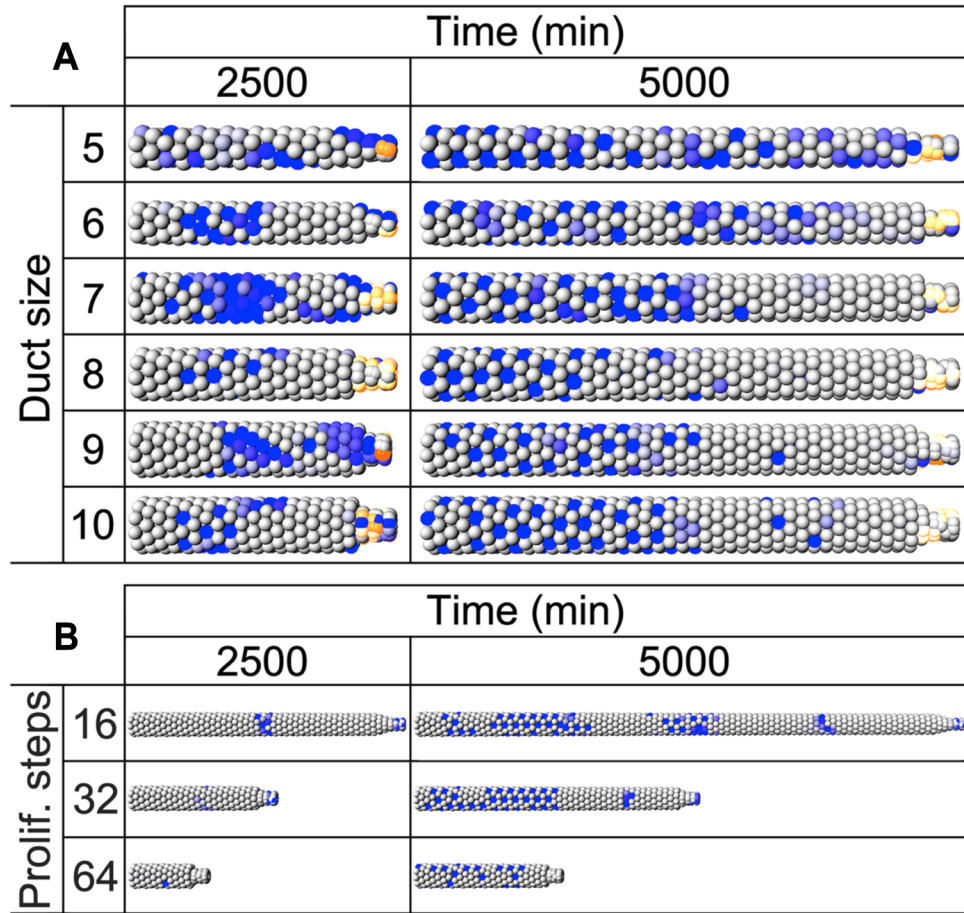
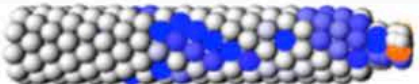
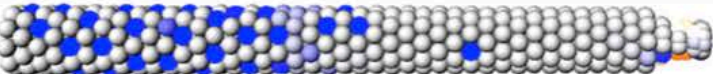
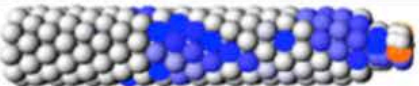
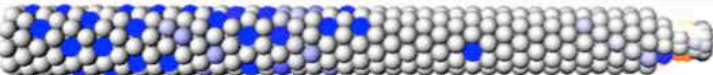
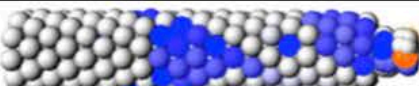
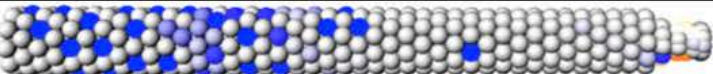
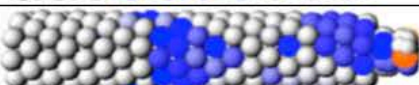
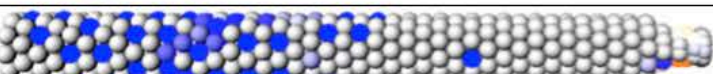
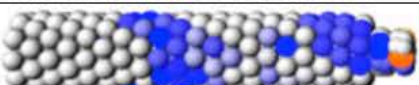
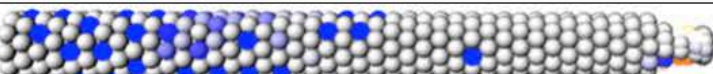
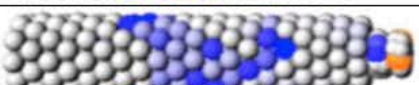
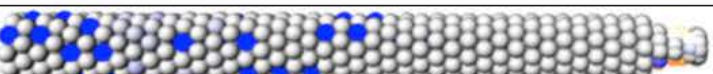

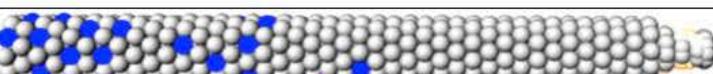

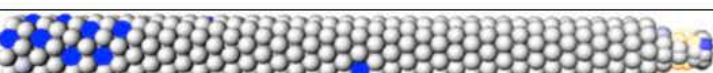
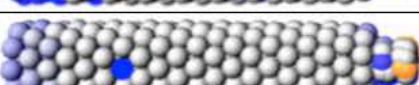



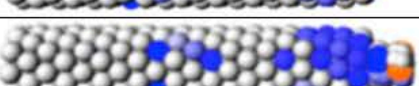
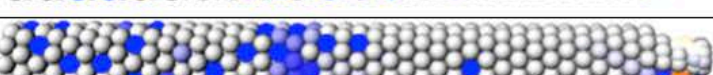
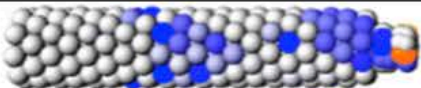
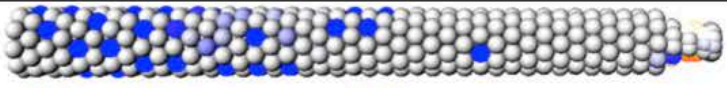
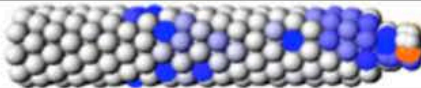
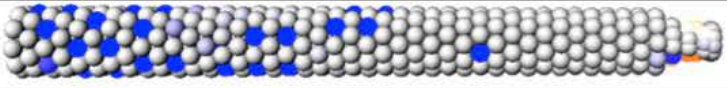
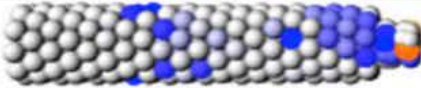
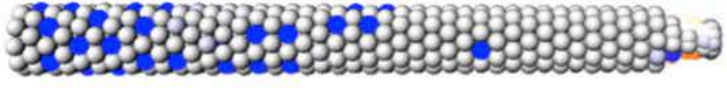

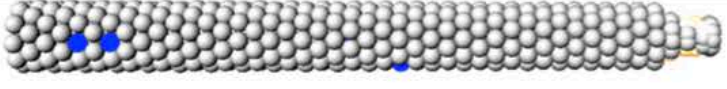

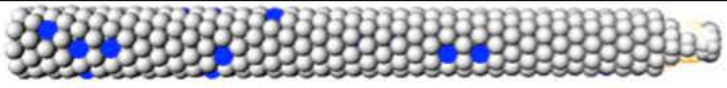
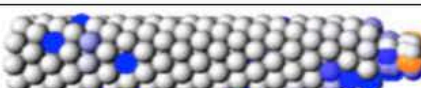
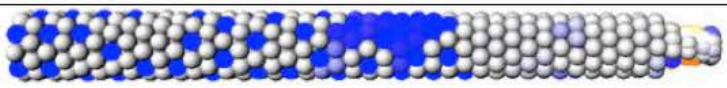

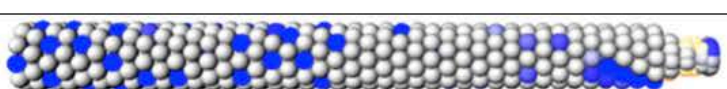

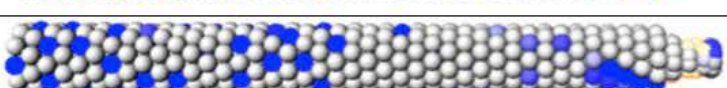
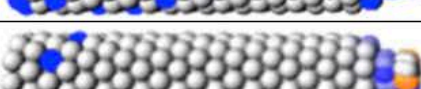
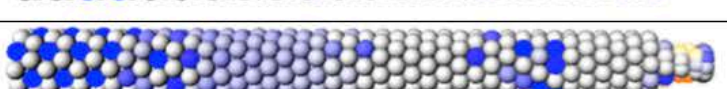




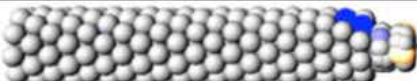
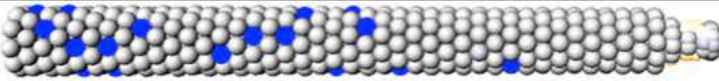
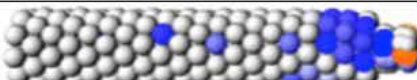
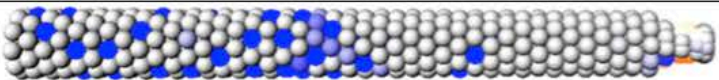
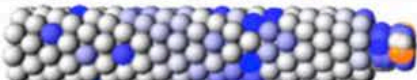
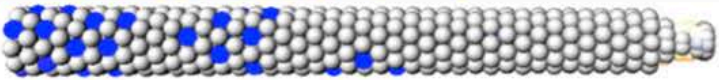

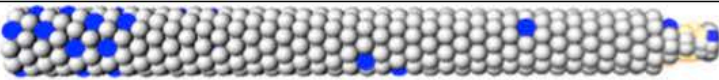

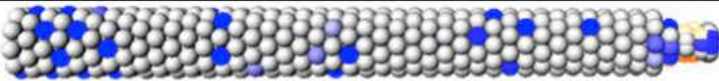

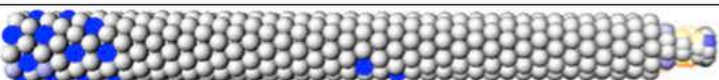
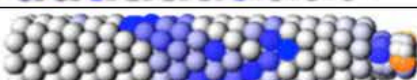
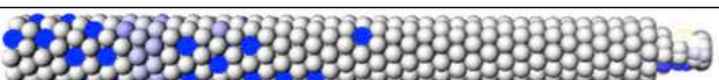
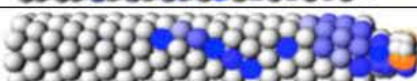
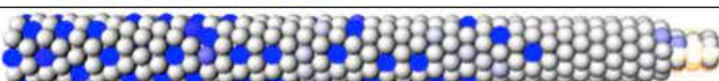
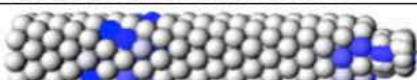
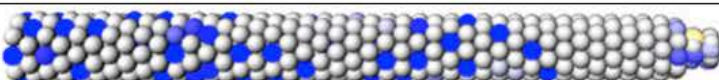
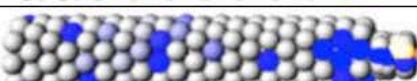
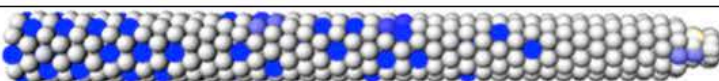
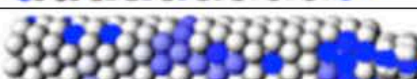
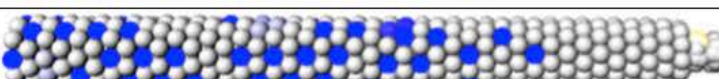
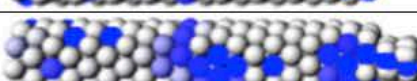
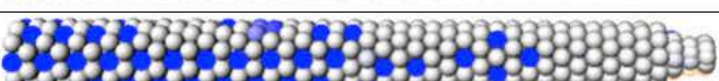


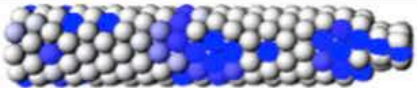
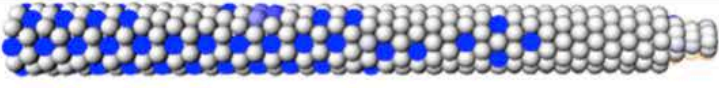
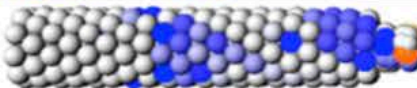
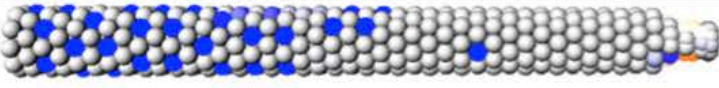
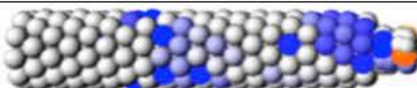
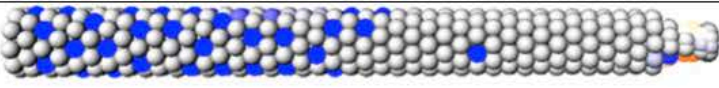
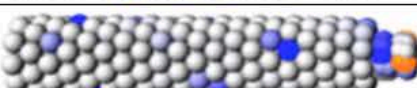
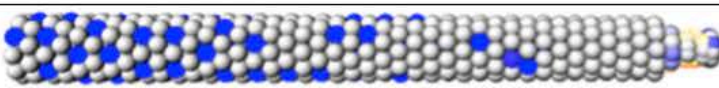
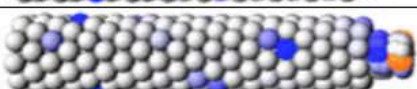
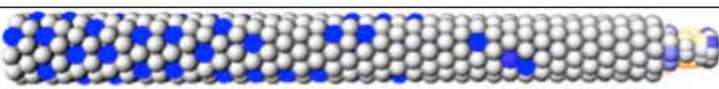
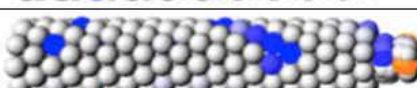
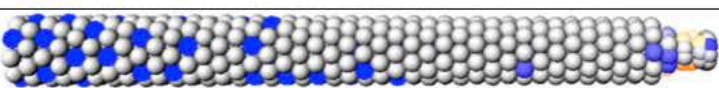

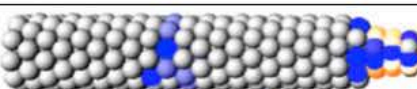
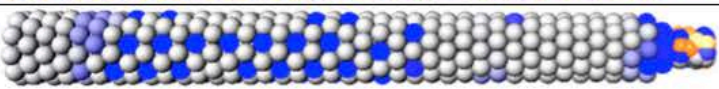
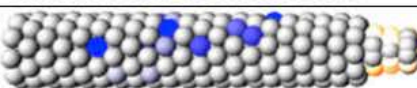
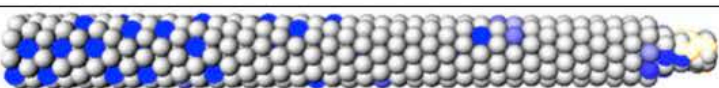
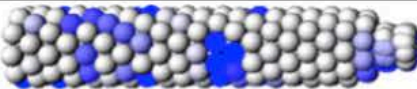
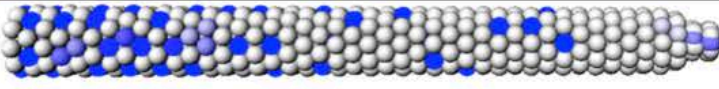
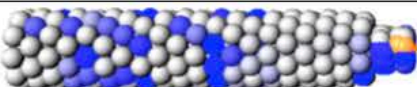
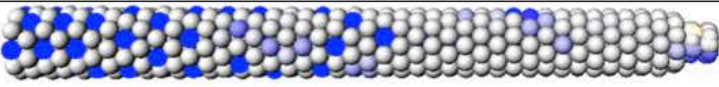
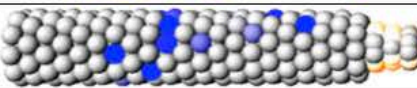
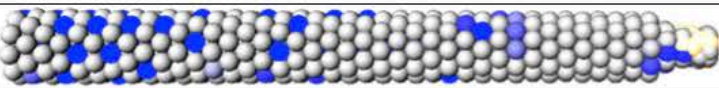
Figure S3. Effect of size and growth rate. Shown are results for a GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3*. (a) The circumference of the duct is varied for different simulations from 5 to 10 cells. Noise is introduced by a transcription stop during mitosis. (b) Variation of duct growth rate. Compared to the default setting (middle row) the growth rate is doubled (top row) or halved (bottom row). Here, initial noise is used, because in the mitosis-growth mode a change in proliferation steps is not linearly translated into a varied growth rate. All snapshots show *Neurog3* mRNA concentration as blue color intensity for each cell. Time points chosen are 2500 and 5000 minutes.

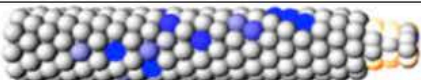
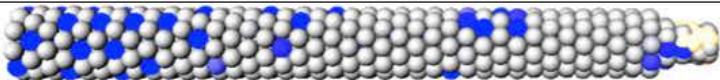
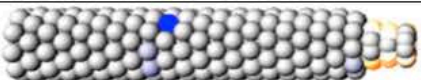
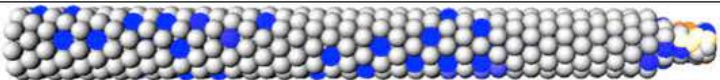
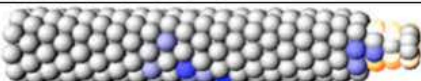
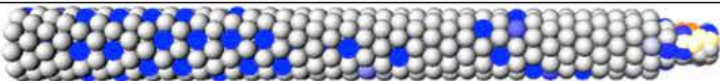
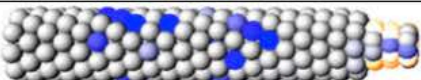
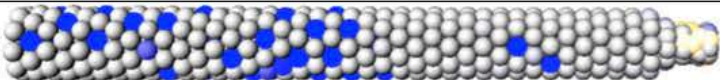
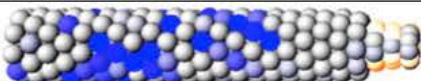
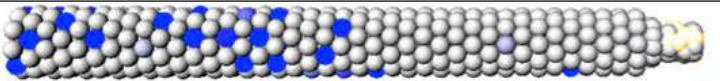
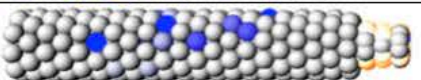
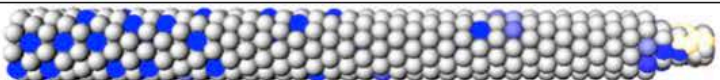
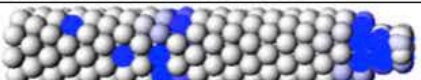
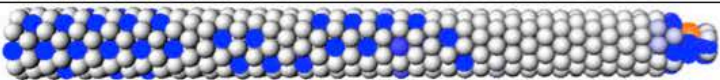

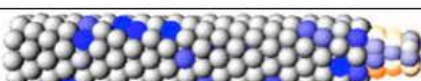
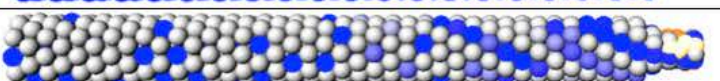
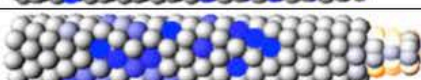
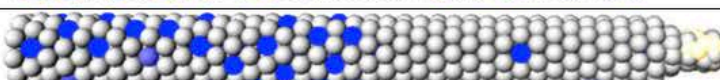

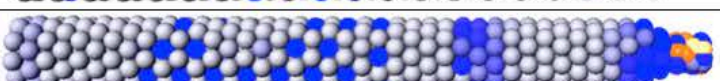


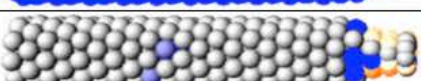
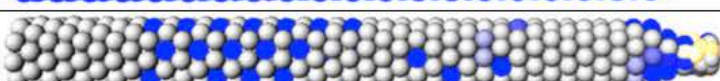
Figure S4. Results for parameter variations for the standard GRN (Fig. 2A). Noise is introduced by a transcription stop during mitosis.

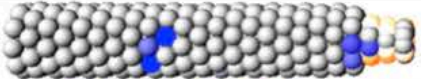
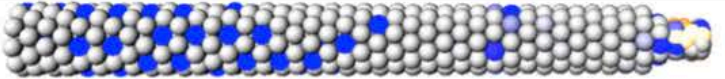
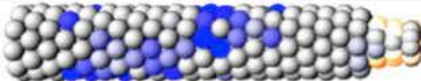
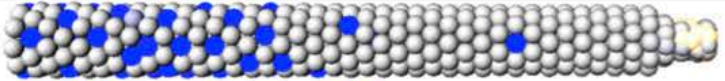
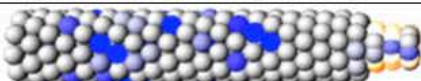
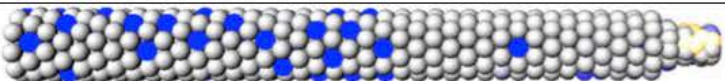
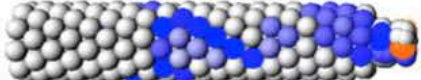
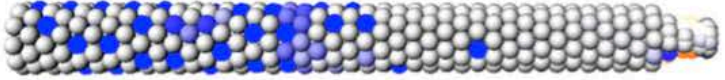
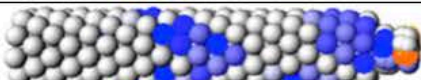
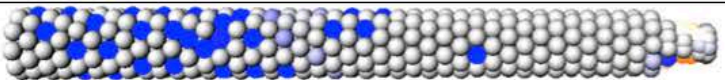
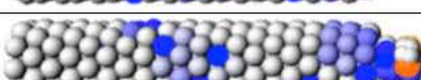

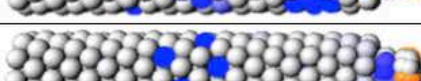
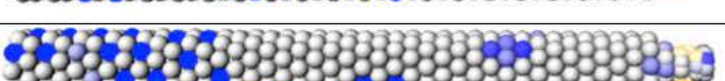
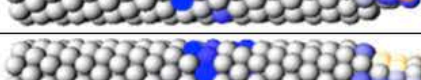
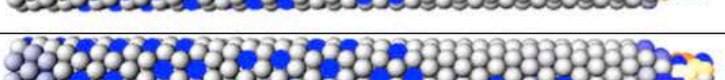
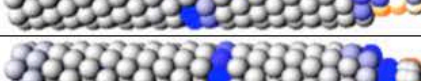
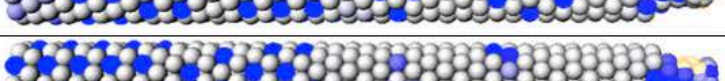
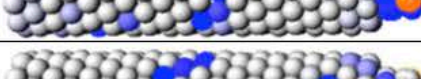
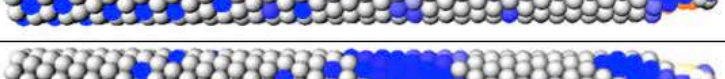
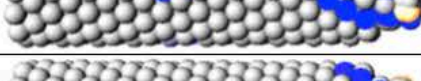
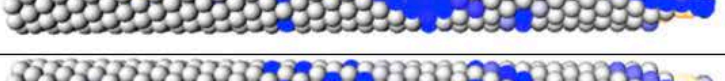

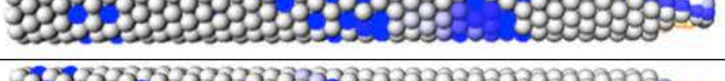
Gene	Parameter	Default value	Value tested	t=2500 min	t=5000 min
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	dmN	0.001	0.0005		
			0.002		
			0.004		
			0.008		
			0.016		
			0.032		
			0.064		
			0.128		
			0.256		
	emN	0.09	0.0225		
			0.045		

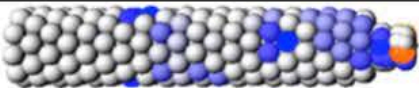
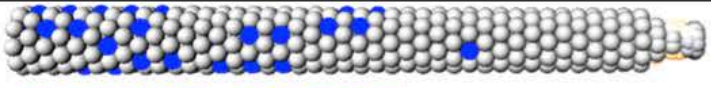
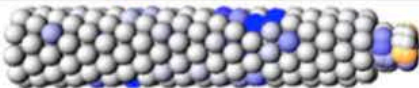
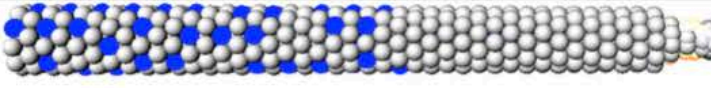
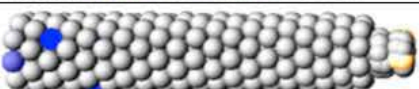
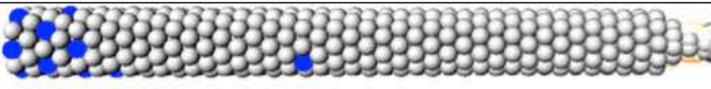
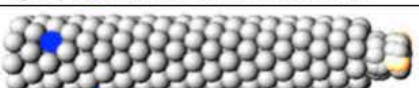
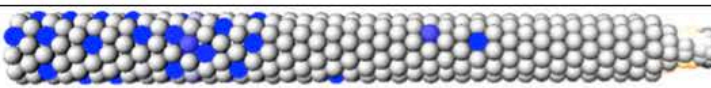
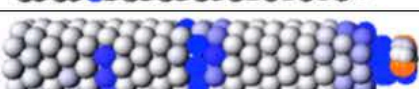
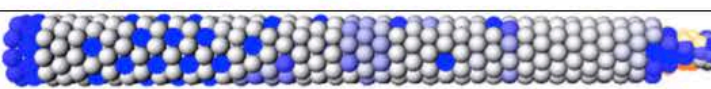



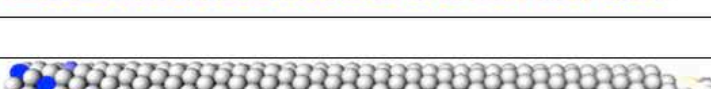
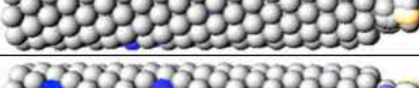
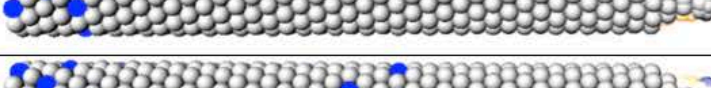
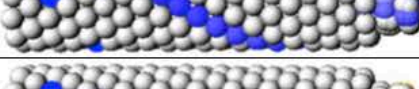
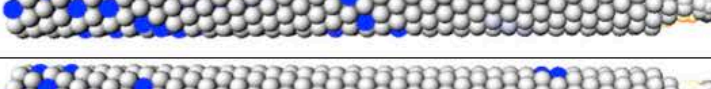
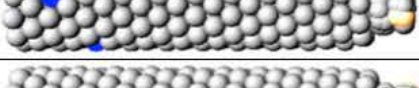
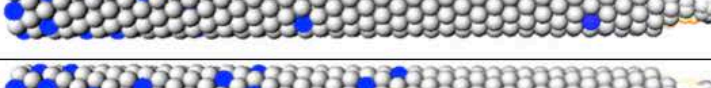
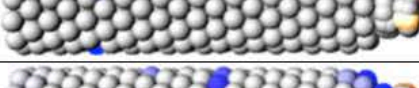
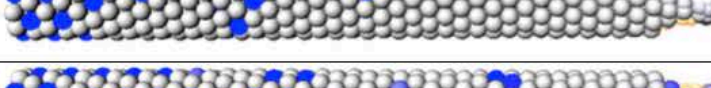
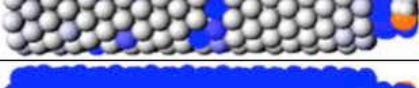

			0.18		
			0.36		
			0.72		
	dmC	0.006	0.0015		
			0.003		
			0.012		
			0.024		
			0.048		
			0.096		
			0.12		
			0.192		



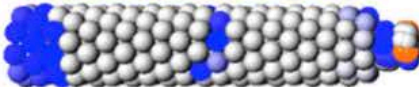
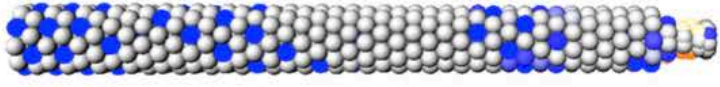
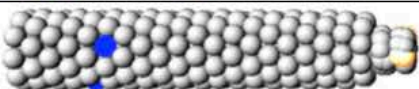
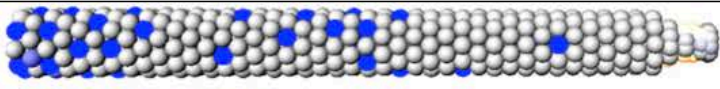
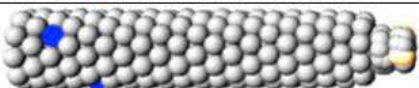
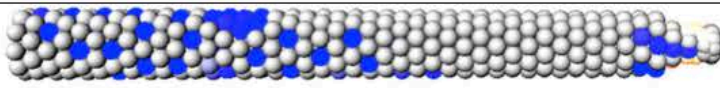
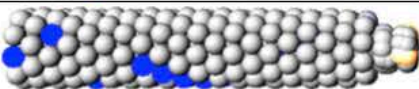
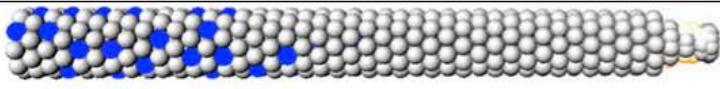
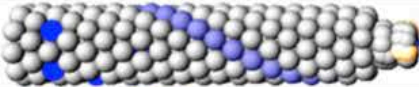
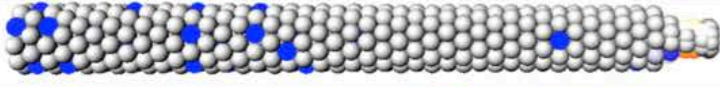
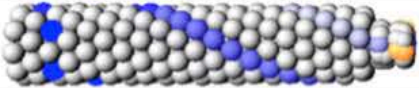
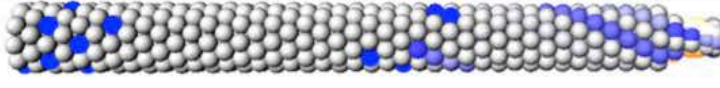
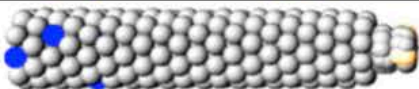
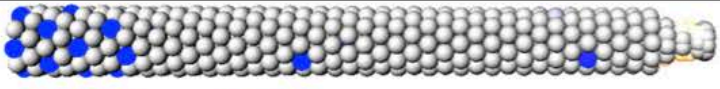
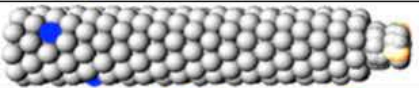
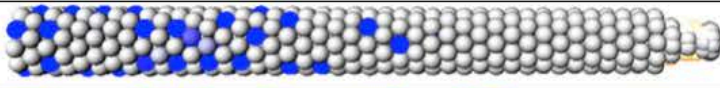
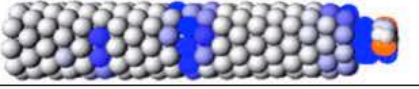
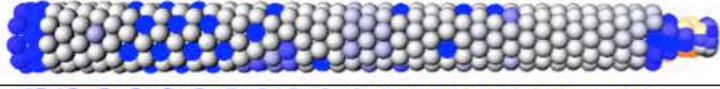
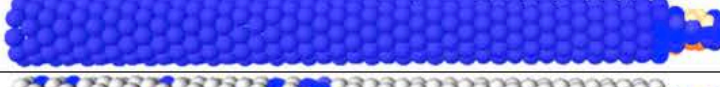


	K	1.5	kept fixed		
	dpC	0.09	0.0025		
			0.005		
			0.2		
			0.4		
			0.8		
	epC	0.1	0.0025		
			0.05		
			0.2		
			0.4		
	epM	0.1	0.025		
			0.05		
			0.2		

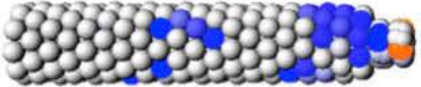
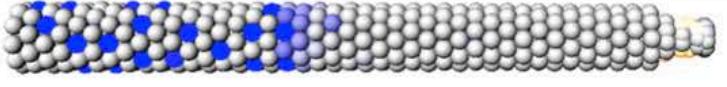
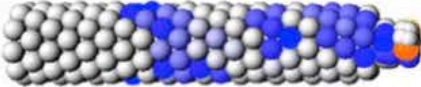
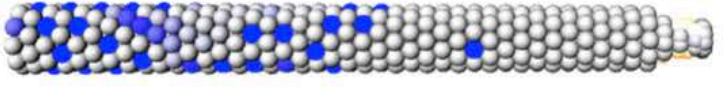
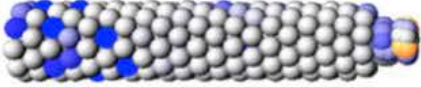
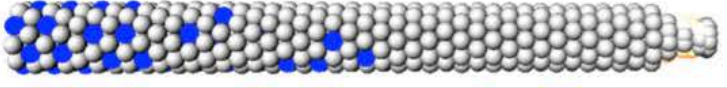
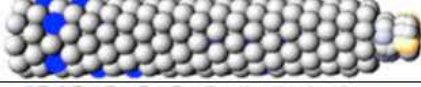
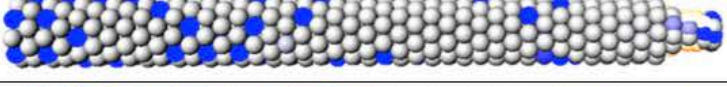
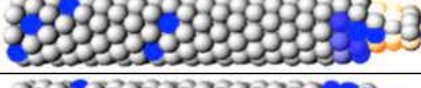
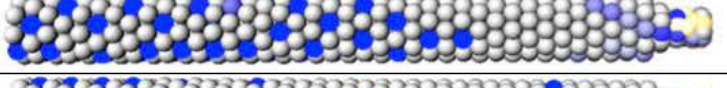
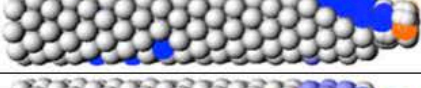
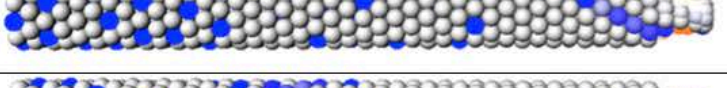
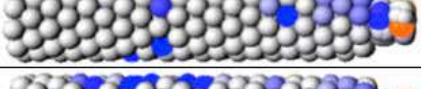
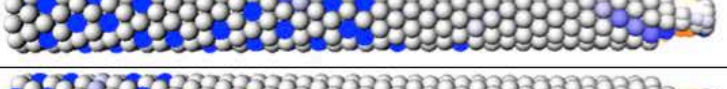
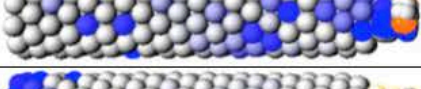
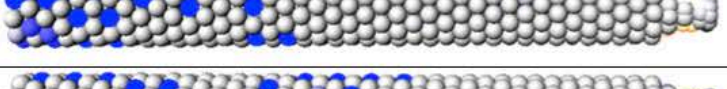
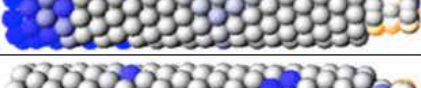
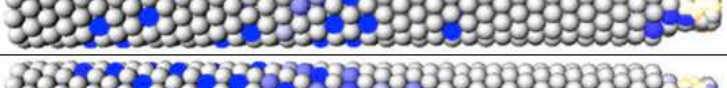

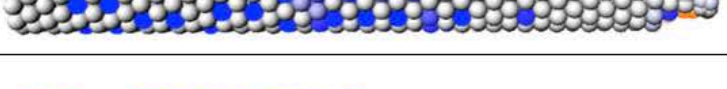
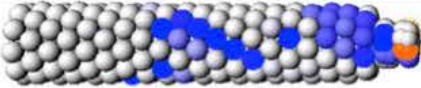
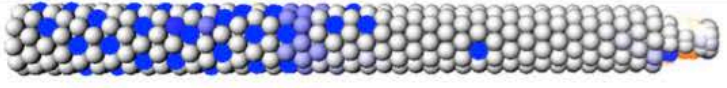
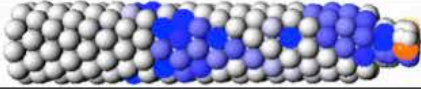
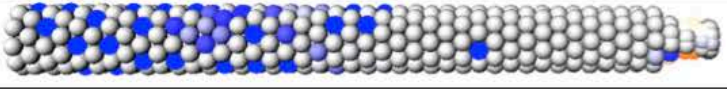
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			0.2		
			0.4		
			0.8		
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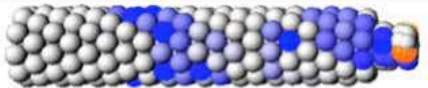
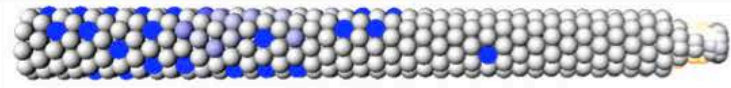
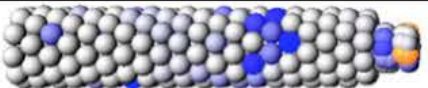
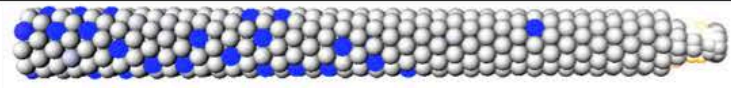
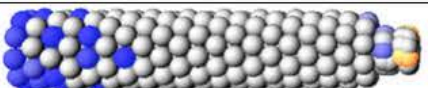
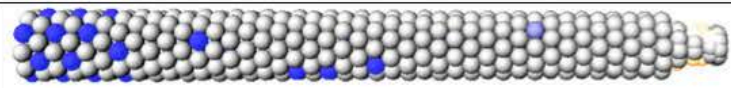
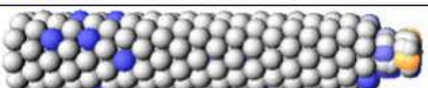
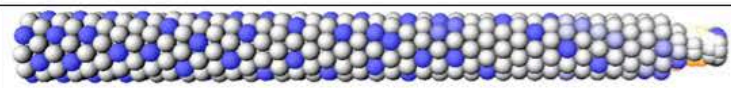

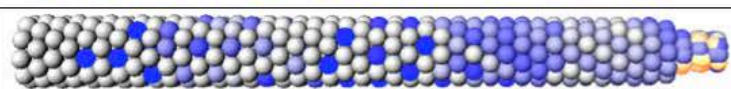

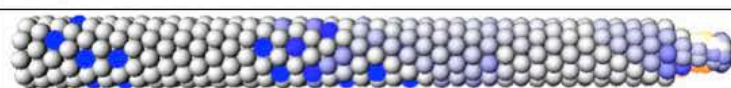
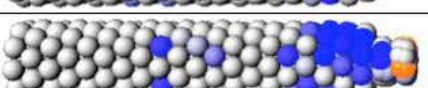
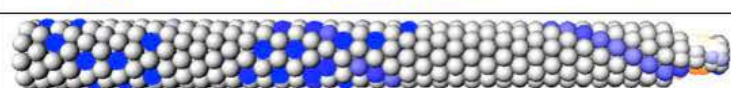
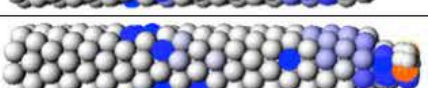
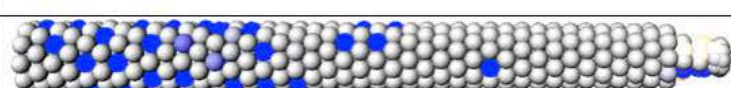
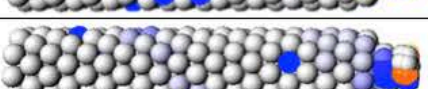
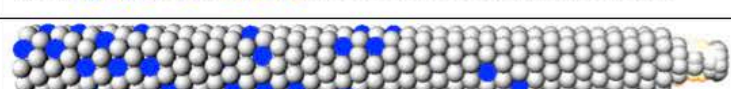
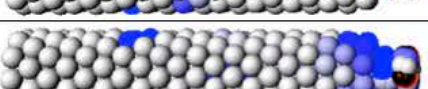

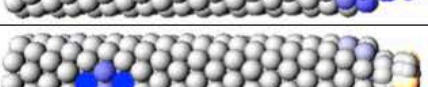
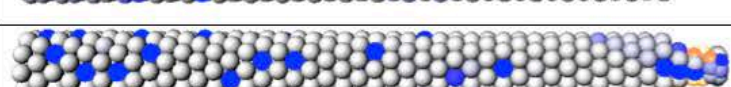
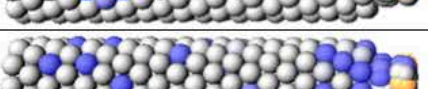
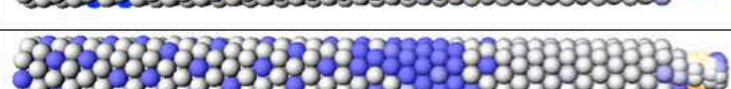
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			0.1		
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			0.4		
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	G	5.0	1.25		
			2.5		
			10.0		
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	F	5.0	1.25		

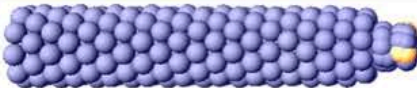
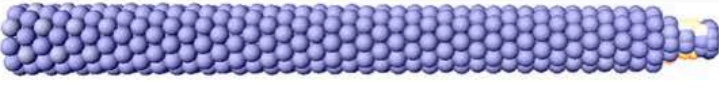
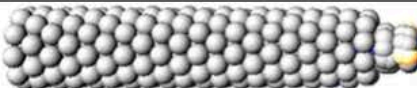
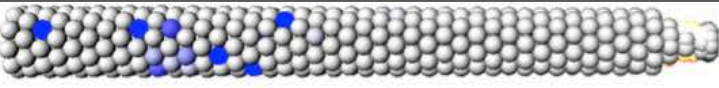
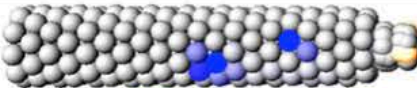
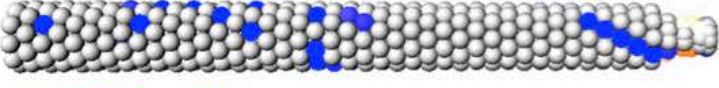
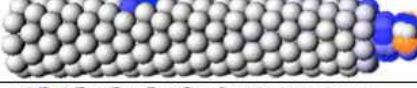
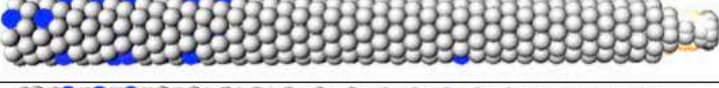
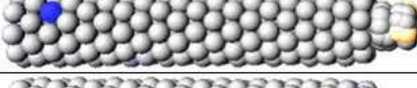
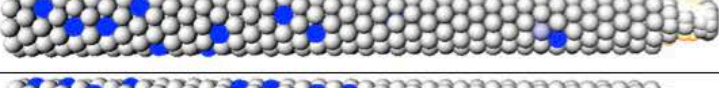
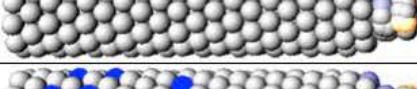
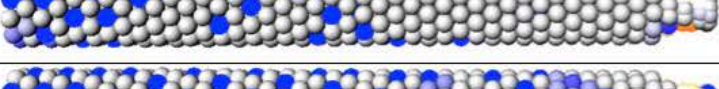
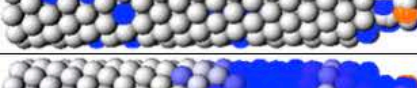
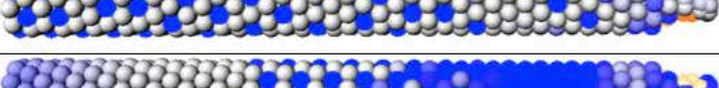
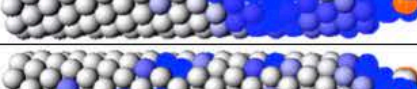
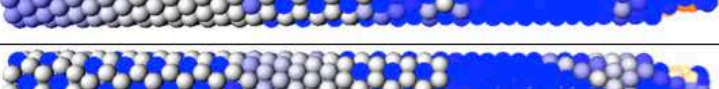
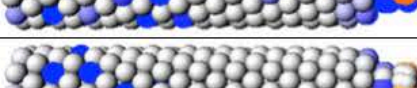
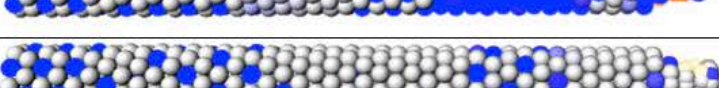
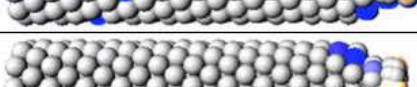
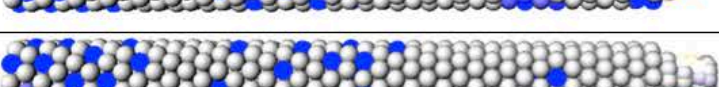
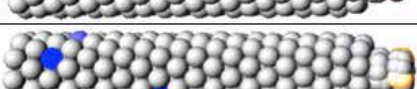
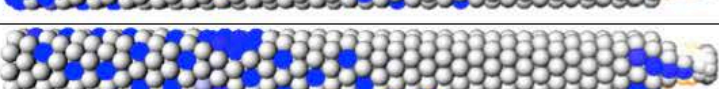
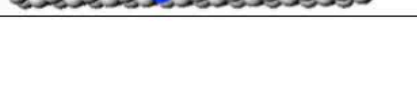

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			10.0		
			20.0		
Hes1	k	0.5	kept fixed		
	dmN	0.001	0.0		
			0.002		
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			0.019		

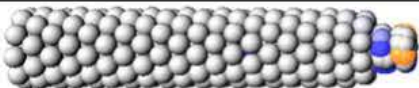
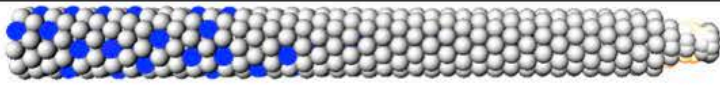
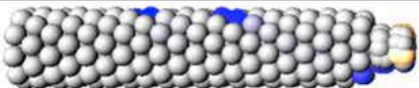
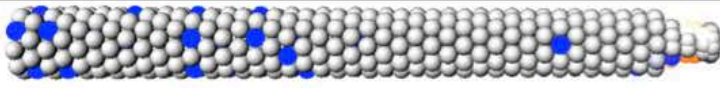
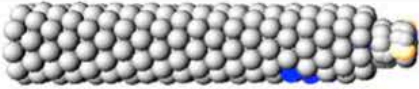
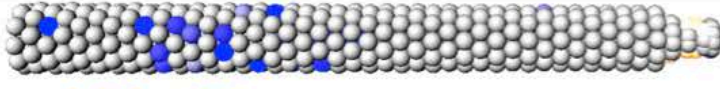
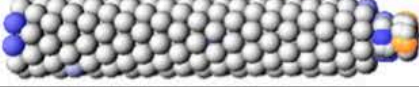
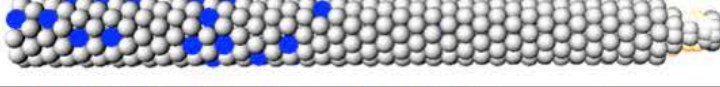
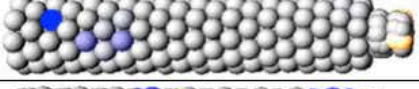
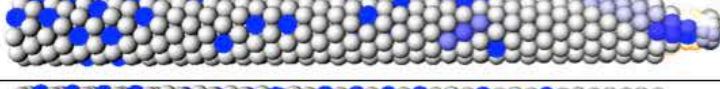
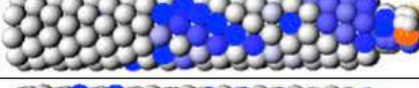
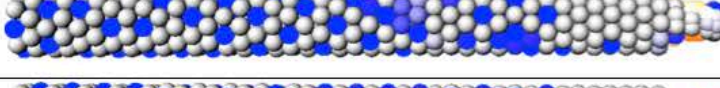
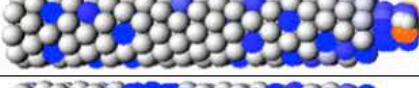
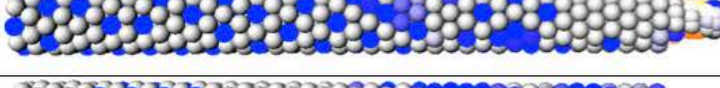
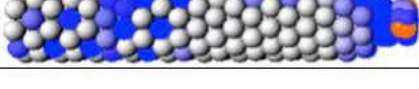
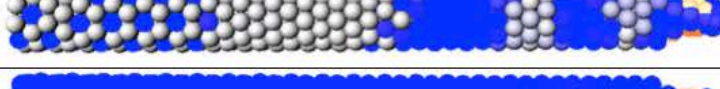

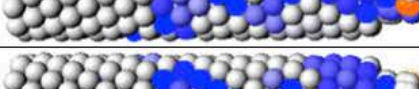
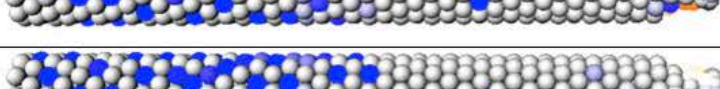
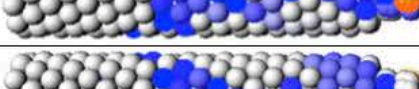
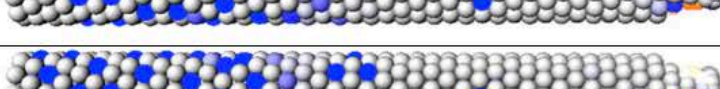
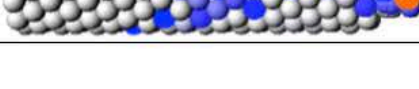
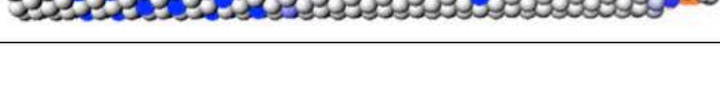
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			0.152		
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			0.034		
			0.134		
			0.268		
	K	1.5	kept fixed		
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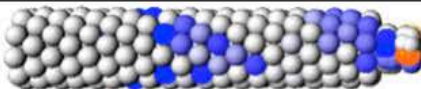
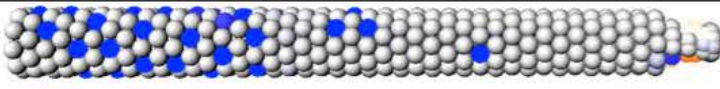
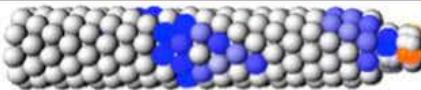
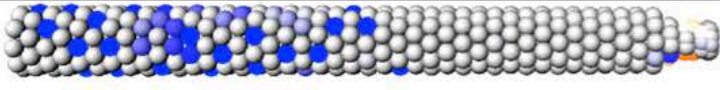
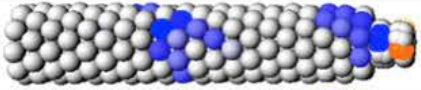
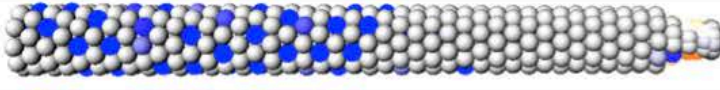
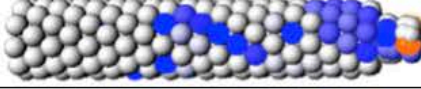
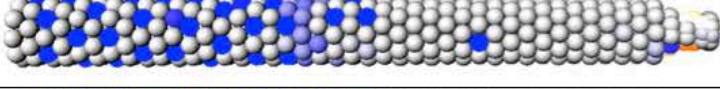
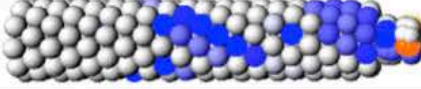
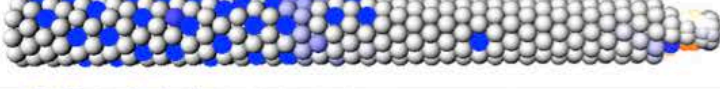
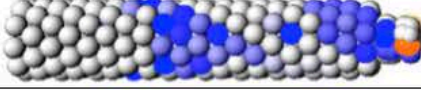
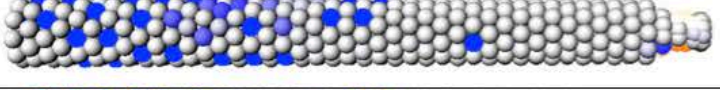
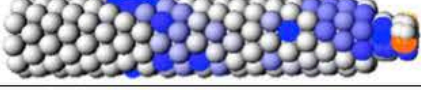
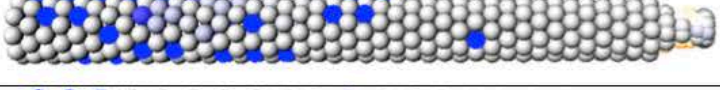
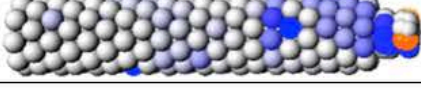
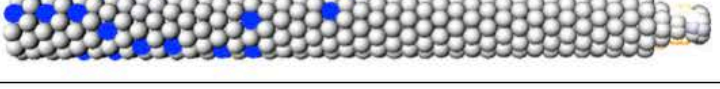
	epC	0.007	0.002		
			0.004		
			0.014		
			0.028		
			0.056		
			0.112		
	G	0.96	0.12		
			0.24		
			0.48		
			1.92		
			2.50		
	F	0.2	0.05		

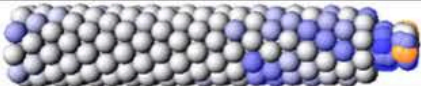
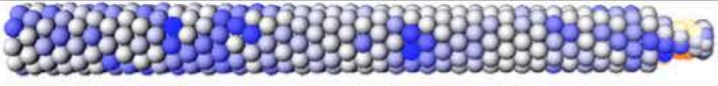
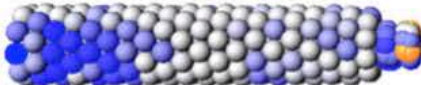
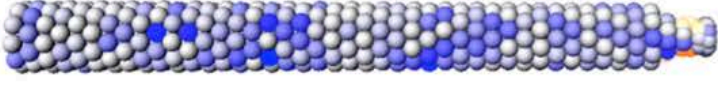
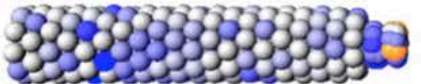
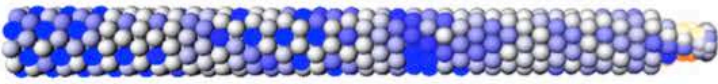

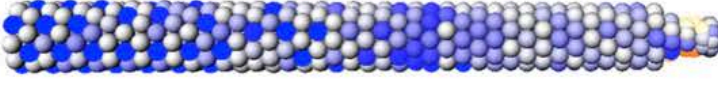

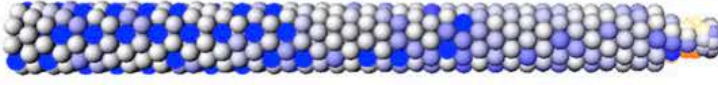
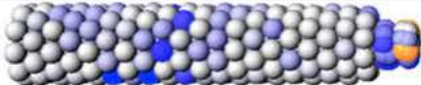
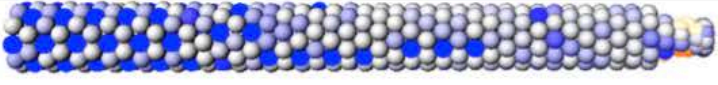
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			0.4		
			0.8		
			1.6		
			3.2		
	epN	0.001	0.0		
			0.0005		
			0.002		
			0.004		
			0.008		
Neurog3	k	0.5	kept fixed		
	dmN	0.001	0.0		
			0.002		

			0.004		
			0.008		
			0.016		
			0.032		
	emN	0.038	0.005		
			0.01		
			0.019		
			0.076		
			0.152		
	dmC	0.067	0.017		
			0.034		
			0.134		

			0.268		
	K	1.5	kept fixed		
	dpC	0.031	0.001		
			0.002		
			0.004		
			0.008		
			0.016		
			0.062		
			0.124		
	epC	0.007	0.002		
			0.004		
			0.014		
			0.028		

			0.056		
			0.112		
	G	0.96	0.12		
			0.24		
			0.48		
			0.96		
			1.92		
			3.0		
			4.0		
	F	0.2	0.05		
			0.1		
			0.4		

			0.8		
			1.6		
			3.2		
	epN	0.001	0.0		
			0.0005		
			0.002		
			0.004		
			0.008		

Hill threshold	t=2500 min	t=5000 min
14.0		
15.0		
15.5		
16.0		
17.0		
18.0		

Variation of the Hill-threshold for the negative feedback of Hes onto its own promoter (see GRN Fig. 7A).

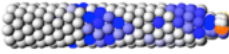
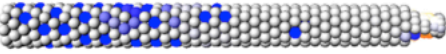
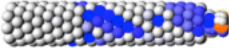
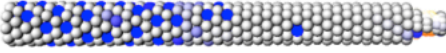
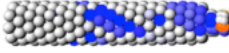
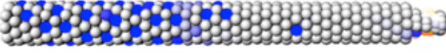
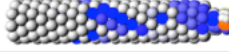
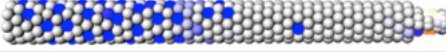
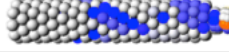

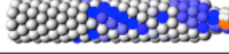
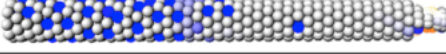
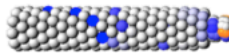
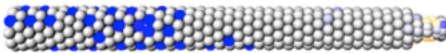
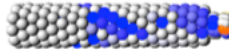
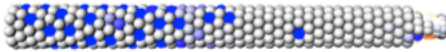
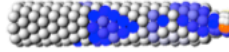
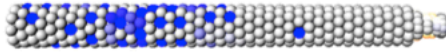
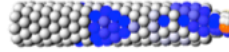
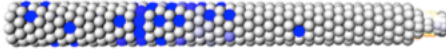

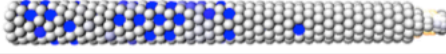


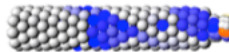
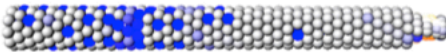
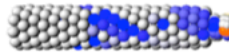
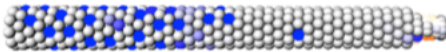
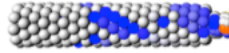
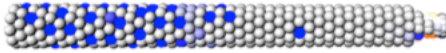
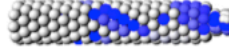
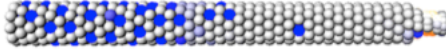
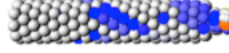
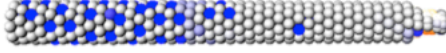
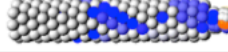

Promoter	Hill coefficient	Time (min)	
		2500	5000
<i>Dll1</i>	1		
	2		
	3		
	4		
	8		
	16		
<i>Hes1</i>	1		
	2		
	3		
	4		
	8		
	16		
<i>Neurog3</i>	1		
	2		
	3		
	4		
	8		
	16		

Figure S5. Variation of the Hill coefficient for *Dll1*, *Hes1*, and *Neurog3*. Shown are results for the standard GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neuorg3*. Noise is introduced by a transcription stop during mitosis.

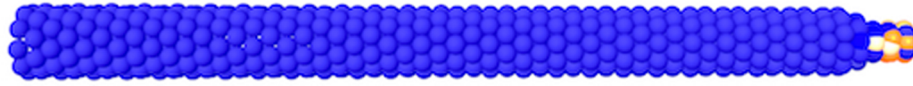


Figure S6. Non-oscillating model with Hes1 negative feedback. Shown is a snapshot of the simulation for a GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3* and itself. Noise is introduced by a transcription stop during mitosis. Halving the *Hes1* transcription rate kills the ultradian oscillations as seen by high *Neurog3* mRNA concentration (in blue color) in all cells.



Figure S7. Simulation runs using delamination for three different GRN topologies. Snap shots were taken every 200 minutes starting at 2,600 min and ending at 5,000 min for the simulation runs as indicated in the respective column.

Gene	Parameter	Abbreviation	Default value
Dll1	transcription rate	k	1.25
	mRNA degradation rate in nucleus	dmN	0.001
	mRNA export rate from nucleus	emN	0.09
	mRNA degradation rate in cytoplasm	dmC	0.006
	translation rate	K	1.5
	protein degradation rate in cytoplasm	dpC	0.09
	protein export rate from cytoplasm	epC	0.1
	export rate from membrane	epM	0.1
	degradation rate in membrane	dpM	0.0
Notch1	transcription rate	k	0.5
	mRNA degradation rate	dm	0.02
	translation rate	K	1.5
	protein degradation rate in cytoplasm	dpC	0.2
	protein export rate from cytoplasm	epC	0.1
	protein degradation rate in membrane	dpM	0.1
	protein export rate from membrane	epM	0.0
NICD	Delta-Notch reaction rate (trans)	r _{DN}	0.05
	export rate from cytoplasm	epC	0.12
	export rate from nucleus	epN	0.06
	protein degradation rate in cytoplasm	dpC	0.2
	protein degradation in nucleus	G	5.0
	protein degradation in nucleus	F	5.0
Hes1	transcription rate	k	0.5
	mRNA degradation rate in nucleus	dmN	0.001
	mRNA export rate from nucleus	emN	0.038
	mRNA degradation rate in cytoplasm	dmC	0.067
	translation rate	K	1.5
	protein degradation rate in cytoplasm	dpC	0.031
	protein export rate from cytoplasm	epC	0.007
	protein degradation in nucleus	G	0.96
	protein degradation in nucleus	F	0.2
Neurog3	protein export rate from nucleus	epN	0.001
	transcription rate	k	0.5
	mRNA degradation rate in nucleus	dmN	0.001
	mRNA export rate from nucleus	emN	0.038
	mRNA degradation rate in cytoplasm	dmC	0.067
	translation rate	K	1.5
	protein degradation rate in cytoplasm	dpC	0.031
	protein export rate from cytoplasm	epC	0.007
	protein degradation in nucleus	G	0.96
	protein degradation in nucleus	F	0.2
	protein export rate from nucleus	epN	0.001

Table S1. Default parameters used for all models, with the single exception for the transcription rate of *Hes1* for the model shown in Fig. S6, which is halved.

Model	GRN	<i>Neurog3</i> promoter	<i>Hes1</i> promoter	<i>Dll1</i> promoter
Pancreas	Fig. 2A	$H_h = R_2(pN_{Hes1})$ $H_R = 1.0$	$H_h = A_2(pN_{NICD})$ $H_A = 4.5$	$H_h = A_2(pN_{Neurog3})$ $H_A = 1.0$
Neurogenesis inspired	Fig. 4A	$H_h = R_2(pN_{Hes1})$ $H_R = 1.0$	$H_h = A_2(pN_{NICD})$ $H_A = 4.5$	$H_h = R_2(pN_{Hes1})$ $A_2(pN_{Neurog3})$ $H_A = 1.0$ $H_R = 1.0$
Somitogenesis inspired	Fig. 5A	$H_h = R_2(pN_{Hes1})$ $H_R = 1.0$	$H_h = A_2(pN_{NICD})$ $H_A = 4.5$	$H_h = R_2(pN_{Hes1})$ $H_R = 1.0$
Pancreas + Hes1 self-feedback	Fig. 6A	$H_h = R_2(pN_{Hes1})$ $H_R = 1.0$	$H_h = R_3(pN_{Hes1})$ $A_2(pN_{NICD})$ $H_A = 4.5$ $H_R = 1.0$	$H_h = A_2(pN_{Neurog3})$ $H_A = 1.0$
Pancreas + weakened Hes1 self-feedback	Fig. 7A	$H_h = R_2(pN_{Hes1})$ $H_R = 1.0$	$H_h = R_3(pN_{Hes1})$ $A_2(pN_{NICD})$ $H_A = 4.5$ $H_R = 16.0$	$H_h = A_2(pN_{Neurog3})$ $H_A = 1.0$

Table S2. Hill-functions and -thresholds describing the promoters of *Dll1*, *Hes1*, and *Neurog3* for the different model variants. *Notch1* expression is constant.

Gene	Parameter	Abbreviation	Default value	Range tested	Lateral inhibition observed
Dll1	transcription rate	k	1.25	kept fixed	
	mRNA degradation rate in nucleus	dmN	0.001	0.0005 – 0.256	0.0005 – 0.256
	mRNA export rate from nucleus	emN	0.09	0.0225 – 0.72	0.0225 – 0.72
	mRNA degradation rate in cytoplasm	dmC	0.006	0.0015 - 0.192	0.003 – 0.096
	translation rate	K	1.5	kept fixed	
	protein degradation rate in cytoplasm	dpC	0.09	0.025 – 0.8	0.025 – 0.8
	protein export rate from cytoplasm	epC	0.1	0.025 – 0.4	0.025 – 0.4
	export rate from membrane	epM	0.1	0.025 – 0.4	0.025 – 0.4
	degradation rate in membrane	dpM	0.0	0.05 – 0.8	0.05 – 0.8
NICD	Delta-Notch reaction rate (trans)	r_DN	0.05	0.0 - 0.05	0.0002 – 0.05
	export rate NICD from cytoplasm	epC	0.12	0.03 – 0.48	0.06 – 0.48
	export rate NICD from nucleus	epN	0.06	0.03 – 0.24	0.03 – 0.24
	protein degradation rate in cytoplasm	dpC	0.2	0.05 – 0.8	0.05 – 0.4
	protein degradation in nucleus	G	5.0	1.25 – 15.0	1.25 – 10.0
	protein degradation in nucleus	F	5.0	1.25 - 20.0	1.25 - 20.0
Hes1	transcription rate	k	0.5	kept fixed	
	mRNA degradation rate in nucleus	dmN	0.001	0.0 – 0.032	0.0 – 0.032
	mRNA export rate from nucleus	emN	0.038	0.005 - 0.3	0.019 – 0.3
	mRNA degradation rate in cytoplasm	dmC	0.067	0.017 – 0.268	0.017 – 0.134
	translation rate	K	1.5	kept fixed	
	protein degradation rate in cytoplasm	dpC	0.031	0.002 – 0.124	0.002 – 0.062
	protein export rate from cytoplasm	epC	0.007	0.002 – 0.112	0.004 – 0.112
	protein degradation in nucleus	G	0.96	0.12 – 4.0	0.12 – 1.92
	protein degradation in nucleus	F	0.2	0.05 – 3.2	0.05 – 3.2

	Protein export rate from nucleus	epN	0.001	0.0 – 0.008	0.0 – 0.008
Neurog3	Transcription rate	k	0.5	kept fixed	
	mRNA degradation rate in nucleus	dmN	0.001	0.0 – 0.032	0.0 – 0.032
	mRNA export rate from nucleus	emN	0.038	0.01 – 0.152	0.01 – 0.152
	mRNA degradation rate in cytoplasm	dmC	0.067	0.017 – 0.268	0.017 - 0.134
	translation rate	K	1.5	kept fixed	
	protein degradation rate in cytoplasm	dpC	0.031	0.001 - 0.124	0.001 – 0.062
	protein export rate from cytoplasm	epC	0.007	0.002 – 0.112	0.004 – 0.112
	protein degradation in nucleus	G	0.96	0.12 – 4.0	0.12 – 1.92
	protein degradation in nucleus	F	0.2	0.05 – 3.2	0.05 – 3.2
	protein export rate from nucleus	epN	0.001	0.0 – 0.008	0.0 – 0.008

Table S3. Model robustness under parameter variation

As Notch1 has constant expression, any change in parameters would in the end change the NOTCH receptor concentration in the membrane compartment. This change could always be reabsorbed into a change of the D/N coupling r_{DN} .

In general, we tried at least two consecutive doublings and halvings of the default value. Not all variations are independently possible. For instance, it is not a meaningful choice when a doubling of the protein export ratio would lead to a much bigger export rate from the nucleus to the cytoplasm, because the protein is a transcription factor and required in the nucleus.

In our program, the concentration values of protein and mRNA are normalized to a range between zero and one. This is achieved by dividing each value by a scaling value near the maximum value in a run. So, it makes no sense to vary transcription or translation rates, because scaling values consequently had to be adjusted for each case anew and the comparability between the visual outputs would be lost.

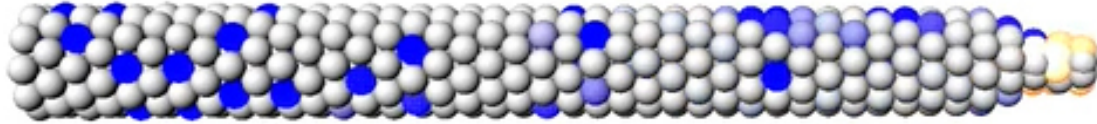
Sensitivity: For *Hes1* and *Neurog3*, emN , epN , dmN as well as F have no big influence on whether lateral inhibition is active or not. The saturated degradation rate in nucleus (G) and the cytoplasmic degradation rates for protein (dpC) and mRNA (dmC) are more sensitive. Too fast degradation rates destroy the lateral inhibition process, which results in uniform *Neurog3* expression.

For NICD, dpC and G respond similar. Too high degradation rates destroy lateral inhibition. Also, a too slow import rate from the cytoplasm into the nucleus hinders NICD signaling and therefore *Hes1* expression and in consequence *Neurog3* suppression.

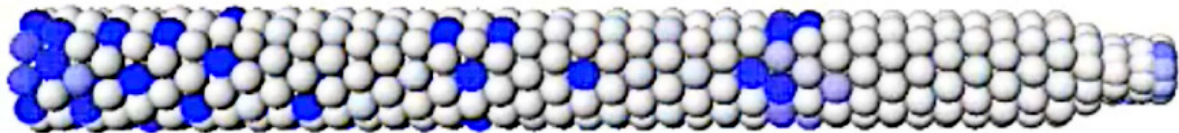
The parameters for *Dll1* are not especially sensitive when varied in our test range. We exceeded the test range in the case of dmC for *Dll1* and increased the value ever more until the fast mRNA decay of 0.12, which we had chosen for our somitogenesis simulations (Tiedemann et al. 2012) to achieve synchronization of the ultradian *Hes7/1* oscillators. Although in this case the *Hes1* negative feedback is not active and wherefore we have no longer transient oscillations, there is a tendency for almost duct-wide synchronization of oscillations. In the further course, this gives way to an inverted lateral inhibition pattern.

SUPPLEMENTAL MOVIES

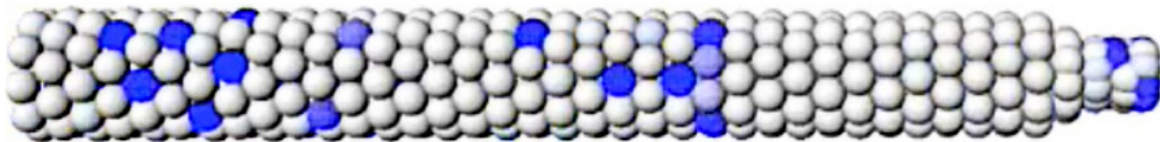
Movie 1. Simulation using the standard GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3*. Noise is introduced by a transcription stop during mitosis.



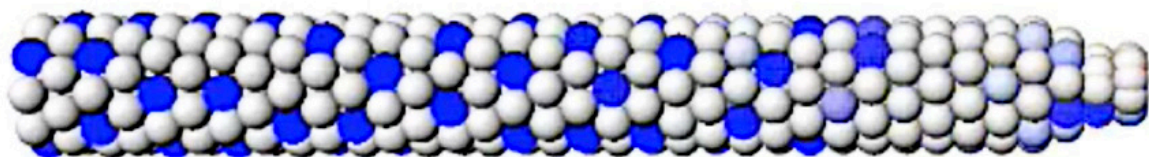
Movie 2. Simulation using initial noise. Shown is the result for the standard GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3*. Noise is introduced by adding random numbers to all concentrations at the start of the simulation.



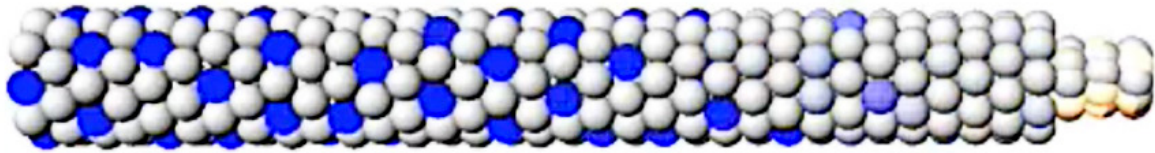
Movie 3. Simulation using stochastic noise. Shown is the result for the standard GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3*. Noise is introduced by simulating the system with chemical Langevin equations.



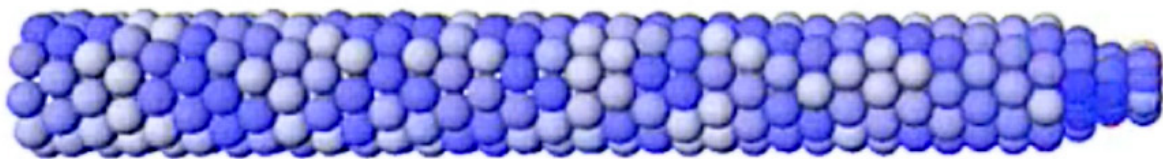
Movie 4. Simulation using a GRN adapted from neurogenesis. Shown is the result for a GRN in which NEUROG3 activates *Dll1* and HES1 inhibits not only *Neurog3* but also *Dll1*. Noise is introduced by a transcription stop during mitosis.



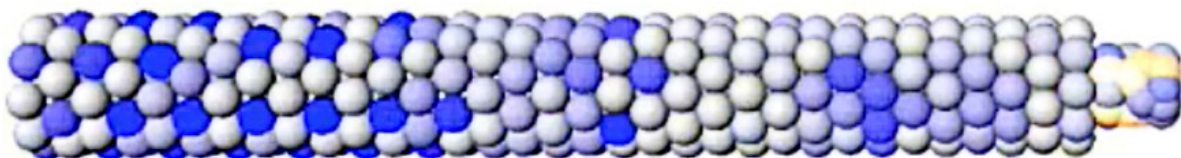
Movie 5. Simulation using a GRN adapted from somitogenesis. Shown is the result for a GRN in which HES1 inhibits *Neurog3* and *Dll1*, but without a positive feedback of NEUROG3 on *Dll1*. Noise is introduced by a transcription stop during mitosis.



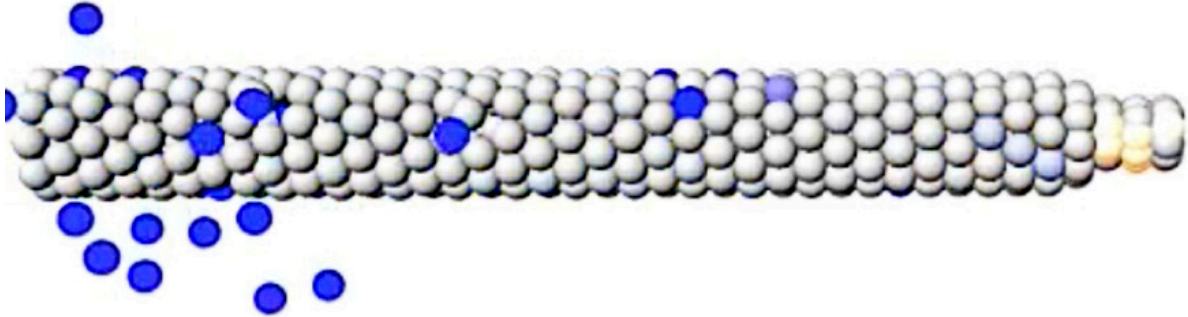
Movie 6. Simulation with negative Hes1 auto-feedback in the standard GRN. Shown is the result for a GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3* and itself. Noise is introduced by a transcription stop during mitosis. The ultradian oscillations prevent lateral-inhibition mediated patterning.



Movie 7. Simulation with weakened negative Hes1-auto-feedback. Shown is the result for a GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3* and weakly its own transcription. Noise is introduced by a transcription stop during mitosis. The simulation starts with ultradian oscillations in all cells and results then in the coexistence of cells with stable *Neurog3* expression, mediated by lateral inhibition, and cells that still show ultradian oscillations.



Movie 8. Simulation using the standard GRN in which NEUROG3 activates *Dll1* and HES1 inhibits *Neurog3*. Noise is introduced by a transcription stop during mitosis. Here, *Snail2* is active downstream of *Neurog3* and effectuates the ablations of cells from the duct when a certain SNAIL2 threshold is exceeded.



Modeling coexistence of oscillation and Delta/Notch-mediated lateral inhibition in pancreas development and neurogenesis

Simulation Program Mini-Manual

System Requirements

We implemented our simulation program as a Java application on a dual core processor machine using jdk1.7 and Java3D version 1.6. To run it we use an amount of 1500MB of the memory allocation pool (java virtual machine options: -Xms1500m -Xmx1500m).

We tested it on

- **Ubuntu 14.04 LTS** with
 - **Java version 1.7**
- **Microsoft Windows 7** with
 - **Java version 1.7**
 - **Java 3D™ pre-release build 1.6.0**
- **Mac OS X 10.10.5** with
 - **Java version 1.7 and 1.8**
 - **Java 3D™ pre-release build 1.6.0** (see below simtool_lib/)
 - **Java™ language bindings to the OpenGL® version 2.2.4** (see below simtool_lib/).

Installation and Starting the Application

To run the application you need to install the packed file SIM15.zip, which can be downloaded from <http://www.helmholtz-muenchen.de/fileadmin/IEG/ZIP/downloads/simulation15/SIM15.zip>.

After unpacking the file you get a directory (*SIM/*) with the following configuration:

- Subdirectory *simtool_lib/* contains the java3d (resp. java bindings to OpenGL) jar files needed to make the application run under Mac OS X 10.10+ (see *SIM/README* for more details) and all other supplementary jar files used by the application.
- Subdirectory *sim_model/PAN* contains the standard configuration file for the gene regulatory network described in the publication and the supplementary material. *Configfile* saves the parameter values needed to start the simulation.
- Executable file *simtool.jar* contains the simulation program.
- Executable batch file *startSimTool.bat* starts the application on **Windows**.
- Executable shell script *startSimTool.sh* starts the application on **Linux** and **Mac OS X**.

Please read the file *SIM/README* for more details.

Starting the Simulation

The application provides a graphical user interface (GUI), on which the parameter values needed to start the simulation can be changed. The buttons to start and stop the simulation are on the bar at the bottom of the GUI:

- By clicking on '**start simulation**' the simulation starts with the configuration status described on the parameter panel (see chapter **Using the Graphical User Interface**).

- Button '**cancel**' terminates the Java application.
- It is possible to return from the simulation panel to the parameter panel by clicking '**return**'.

Using the Graphical User Interface (GUI)

The picture below shows the part of the GUI containing information about the genes building the gene regulatory network (GRN) and its interactions.

gene	geneprod	visible	color	scaling	prom	prom_hc	prom_critval	prom_term	initial	initnoise	d	d_basic	G	F	d_grad	k	K	K_grad	ex	ex_grad	cis	trans
<input checked="" type="checkbox"/> Dll1	<input type="checkbox"/> ko	mC	<input type="checkbox"/> blue	9.0	<input checked="" type="checkbox"/> Neur...	2.0	1.0	$pN^{2.0} / (1 + pN^{2.0})$	1.0	<input checked="" type="checkbox"/>	0.006				<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10							
		mN	<input type="checkbox"/> blue	13.0	<input type="checkbox"/> Hes1	2.0	1.0	$1 / (1 + pN^{2.0})$	5.0	<input checked="" type="checkbox"/>	0.001				<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10	1.25			0.09			
		pC	<input type="checkbox"/> red	2.5	<input type="checkbox"/> Wnt3a	1.0	1.0	$p / (1 + p)$	5.0	<input checked="" type="checkbox"/>	0.09				<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10		1.5		0.1		0.0	
		pM	<input type="checkbox"/> red	1.0	<input type="checkbox"/> Ptf1a	3.0	10.0	$(pN / 10.0)^{3.0} / (1 + (pN / 10.0)^{3.0})$	5.0	<input checked="" type="checkbox"/>	0.0				<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10				0.1		0.0	0.05
<input checked="" type="checkbox"/> Notch1	<input type="checkbox"/> ko	m	<input type="checkbox"/> blue	25.0	<input type="checkbox"/> Wnt3a	3.0	10.0	$(p / 10.0)^{3.0} / (1 + (p / 10.0)^{3.0})$	10.0	<input checked="" type="checkbox"/>	0.02				<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10	0.5						
		pC	<input type="checkbox"/> red	52.0					10.0	<input checked="" type="checkbox"/>	0.2				<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10		1.5		0.1		0.0	
		pM	<input type="checkbox"/> red	52.0					5.0	<input checked="" type="checkbox"/>	0.1				<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10				0.0		0.0	0.05
<input type="checkbox"/> NICD	<input type="checkbox"/> ko	pC	<input type="checkbox"/> red	25.0					5.0	<input checked="" type="checkbox"/>	0.2	0.02			<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10				0.12			
		pM	<input type="checkbox"/> red	50.0					5.0	<input checked="" type="checkbox"/>			5.0	5.0	<input type="checkbox"/> Wnt3a <input type="checkbox"/> Fgf10				0.06			
<input checked="" type="checkbox"/> Hes1	<input type="checkbox"/> ko	mC	<input type="checkbox"/> blue	5.0	<input type="checkbox"/> Hes6	3.0	1.0	$1 / (1 + pN^{3.0})$	0.0	<input checked="" type="checkbox"/>	0.067				<input type="checkbox"/> Fgf10							

- The cells of the genes table are editable

gene	geneprod	visible	color	scaling	prom	prom_hc	prom_critval	prom_term	initial	initnoise	d	d_basic	G	F
<input checked="" type="checkbox"/> Dll1	<input type="checkbox"/> ko	mC	<input type="checkbox"/> blue	9.0	<input checked="" type="checkbox"/> Neur...	2.0	1.0	$pN^{2.0} / (1 + pN^{2.0})$	1.0	<input checked="" type="checkbox"/>	0.006			
		mN	<input type="checkbox"/> blue	13.0	<input type="checkbox"/> Hes1	2.0	1.0	$1 / (1 + pN^{2.0})$	5.0	<input checked="" type="checkbox"/>	0.001			
		pC	<input type="checkbox"/> red	2.5	<input type="checkbox"/> Wnt3a	1.0	1.0	$p / (1 + p)$	5.0	<input checked="" type="checkbox"/>	0.09			
		pM	<input type="checkbox"/> red	1.0	<input type="checkbox"/> Ptf1a	3.0	10.0	$(pN / 10.0)^{3.0} / (1 + (pN / 10.0)^{3.0})$	5.0	<input checked="" type="checkbox"/>	0.0			

- The '**initial noise**' is a simple measure for the initial noise, i.e. by selecting the '**initnoise**'-option in the table we add to the initial concentration value the entered (percentage) value of the initial value multiplied by a random value between zero and one.

scaling	prom	prom_hc	prom_critval	prom_term	initval	initnoise
9.0	<input checked="" type="checkbox"/> Neur...	2.0	1.0	$pN^{2.0} / (1 + pN^{2.0})$	1.0	<input checked="" type="checkbox"/>
13.0	<input type="checkbox"/> Hes1	2.0	1.0		5.0	<input checked="" type="checkbox"/>
2.5	<input type="checkbox"/> Wnt3a	1.0	1.0		5.0	<input checked="" type="checkbox"/>
1.0	<input type="checkbox"/> Ptf1a	3.0	10.0	$(pN / 10.0)^{3.0} / (1 + (pN / 10.0)^{3.0})$	5.0	<input checked="" type="checkbox"/>
25.0	<input type="checkbox"/> Wnt3a	3.0	10.0	$(p / 10.0)^{3.0} / (1 + (p / 10.0)^{3.0})$	10.0	<input checked="" type="checkbox"/>
52.0					10.0	<input checked="" type="checkbox"/>
52.0						<input checked="" type="checkbox"/>
5.0						<input checked="" type="checkbox"/>

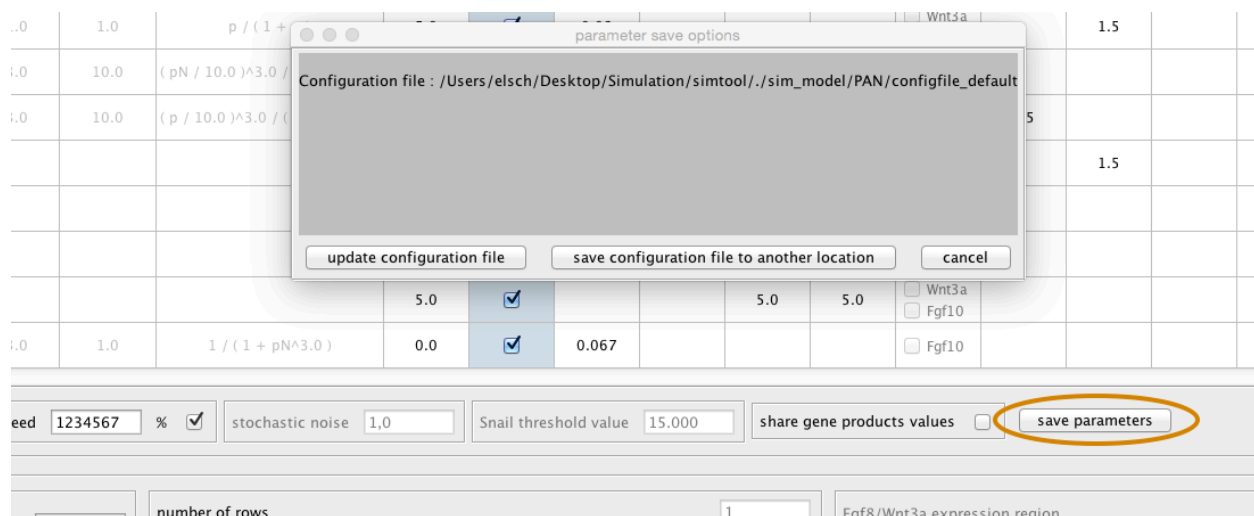
initial noise enabled for gene product

start with initial noise means:
 $\langle \text{initval} \rangle = \langle \text{initval} \rangle + \langle \text{random value} \rangle * \langle \text{initial noise} \rangle$

initial noise percent enabled means:
 $\langle \text{initval} \rangle = \langle \text{initval} \rangle * (1 + \langle \text{random value} \rangle * \langle \text{initial noise} \rangle)$

initial noise 30 seed 1234567 % ☒ stochastic noise 1,0 Snail thresh

- By clicking '**save parameters**' an update of the configuration file *sim_model/<model_description>/configfile* occurs. All modifications made on the GUI can be thus used by another program run. The old configuration file will be moved to *OLD/configfile.OLD<index>*.



- All network **genes** are described in the genes table. The parameters of each gene can be accessed by editing the corresponding cells in the table.

- Gene **excluded from network** means that no computation would be done for its products. In case of Delta-Notch genes the elimination of **Dll1** (**Notch1**) from the GRN implies also the elimination of **Notch1** (**Dll1**) and **NICD**.

gene regulatory network

gene	geneprod	visible	color	scaling	prom
<input type="checkbox"/> Dll1 <input type="checkbox"/> ko					
<input checked="" type="checkbox"/> Notch1 <input type="checkbox"/> ko	m	<input type="checkbox"/>	blue	25.0	<input type="checkbox"/> Wnt
			red	52.0	
			red	52.0	
NICD				25.0	
				50.0	
<input checked="" type="checkbox"/> Hes1 <input type="checkbox"/> ko	mC	<input type="checkbox"/>	blue	5.0	<input type="checkbox"/> Hes
	mN	<input type="checkbox"/>	blue	12.0	<input type="checkbox"/> Hes

exclude gene from gene regulatory network if gene check box not selected

- We simulate a **gene knock out** by setting the mRNA transcription rate to 0.

gene regulatory network

gene	geneprod	visible	color	scaling	prom	prom_hc	prom
<input type="checkbox"/> Dll1 <input type="checkbox"/> ko							
<input checked="" type="checkbox"/> Notch1 <input type="checkbox"/> ko	m	<input type="checkbox"/>	blue	25.0	<input type="checkbox"/> Wnt3a	3.0	
	pC	<input type="checkbox"/>	red	52.0			
NICD <input type="checkbox"/> ko							
<input checked="" type="checkbox"/> Hes1 <input checked="" type="checkbox"/> ko	mC	<input type="checkbox"/>	blue	5.0	<input type="checkbox"/> Hes6	3.0	
	mN	<input type="checkbox"/>	blue	12.0	<input type="checkbox"/> Hes1	3.0	
	pC	<input type="checkbox"/>	red	160.0	<input type="checkbox"/> NICD	2.0	
	pN	<input type="checkbox"/>	red	10.0			

select „ko“ to simulate a knock out of the corresponding gene

- Select the gene product to be visualized during simulation.

gene	geneprod	visible	color	scaling	prom	prom_hc	prom_critval	prom_term
<input type="checkbox"/> Hes6 <input type="checkbox"/> ko								
<input type="checkbox"/> Nkx6-1 <input type="checkbox"/> ko								
<input checked="" type="checkbox"/> Neur... <input type="checkbox"/> ko	mC	<input checked="" type="checkbox"/>	blue	7.0				
	mN		blue		<input type="checkbox"/> Hes1	2.0	100.0	$1 / (1 + (pN / 100.0$
	pC		red	300.0				
	pN		red	1200.0				
<input type="checkbox"/> Ptf1a								
<input type="checkbox"/> Snail								
<input type="checkbox"/> Fgf10 <input type="checkbox"/> ko								
<input type="checkbox"/> Wnt3a <input type="checkbox"/> ko								

- The genes table contains also information about gene promoters.

prom	prom_hc	prom_critval	prom_term	in
<input checked="" type="checkbox"/> Neurog3	2.0	1.0	$pN^{2.0} / (1 + pN^{2.0})$	
<input type="checkbox"/> Hes1	2.0	1.0	$1 / (1 + pN^{2.0})$	
<input type="checkbox"/> Ptf1a	3.0	10.0	$p / (1 + p)$	
<input type="checkbox"/> Wnt3a	3.0		$(0.0)^{3.0} / (1 + (pN \dots$	
			$(0.0)^{3.0} / (1 + (p / 1 \dots$	
<input type="checkbox"/> Hes6	3.0	1.0	$1 / (1 + pN^{3.0})$	

Select the '**mitosis**' check box to simulate **mitosis**, which is done by setting the transcription rate to 0 for the selected genes. During the simulation the cells undergoing mitosis are colored orange.

initial noise 0 seed 1234567 % stochastic noise 1.0 Snail threshold value 15.000 share gene products values save parameters

simulation parameters

total number of steps 60.000

time step in minutes 0.1

time steps between rendering 30

mitosis ☒

duration of mitosis in rendering steps 15

duration of S-Phase in rendering steps 10

plot cells ☐

number of rows 1

number of cells on row 9

number of cell layers 1

initial number of cells 9

maximal number of cells 500

initial position

x -1.0

y -0.25

z -0.25

Fgf8/Wnt3a expression region 1

duct form ☒

diagonal form ☐

maximal number of cell neighbors 6

proliferation region 2

proliferation seed 1.234.567

number of proliferation steps 32

proliferation direction

phi 270

theta 50

select type of differential equations visualize start simulation plot data cancel

The lower part of the GUI is reserved for general settings like the layout of the proliferating cells and the way they proliferate.

initial noise 0 seed 1234567 % stochastic noise 1.0 Snail threshold value 15.000 share gene products values save parameters

simulation parameters

total number of steps 60.000

time step in minutes 0.1

time steps between rendering 30

mitosis ☒

duration of mitosis in rendering steps 15

duration of S-Phase in rendering steps 10

plot cells ☐

number of rows 1

number of cells on row 9

number of cell layers 1

initial number of cells 9

maximal number of cells 500

initial position

x -1.0

y -0.25

z -0.25

Fgf8/Wnt3a expression region 1

duct form ☒

diagonal form ☐

maximal number of cell neighbors 6

proliferation region 2

proliferation seed 1.234.567

number of proliferation steps 32

proliferation direction

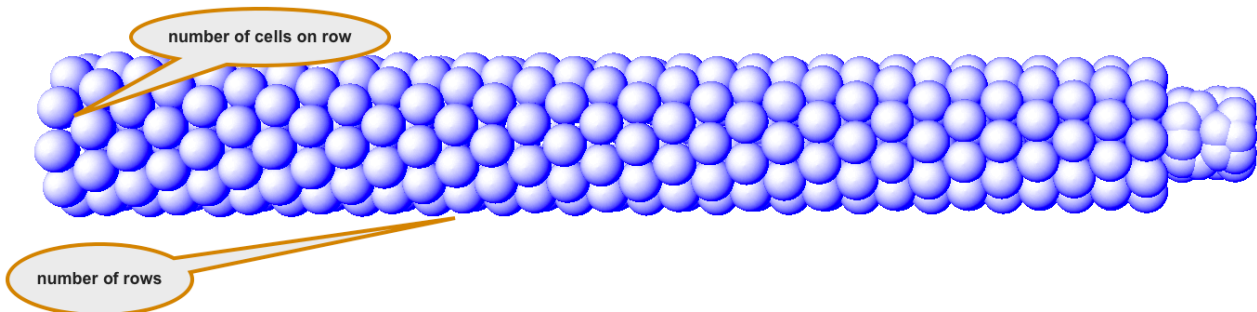
phi 270

theta 50

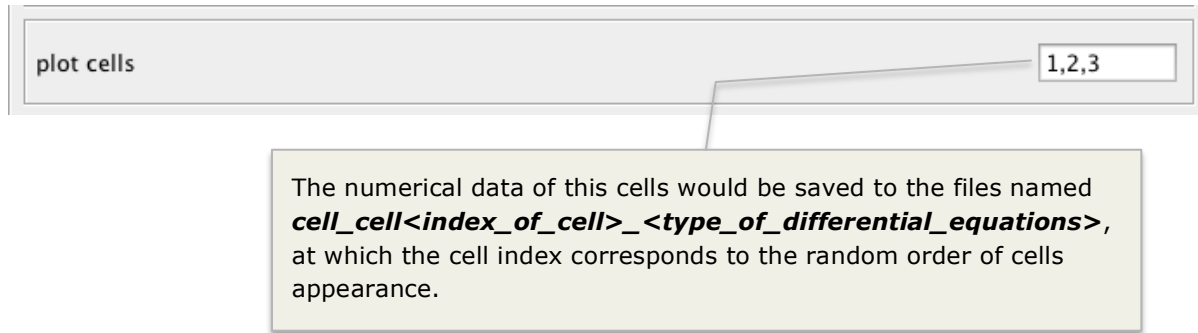
new cells take over the gene products values of the parent cells

defines the position of the initial configuration of cells

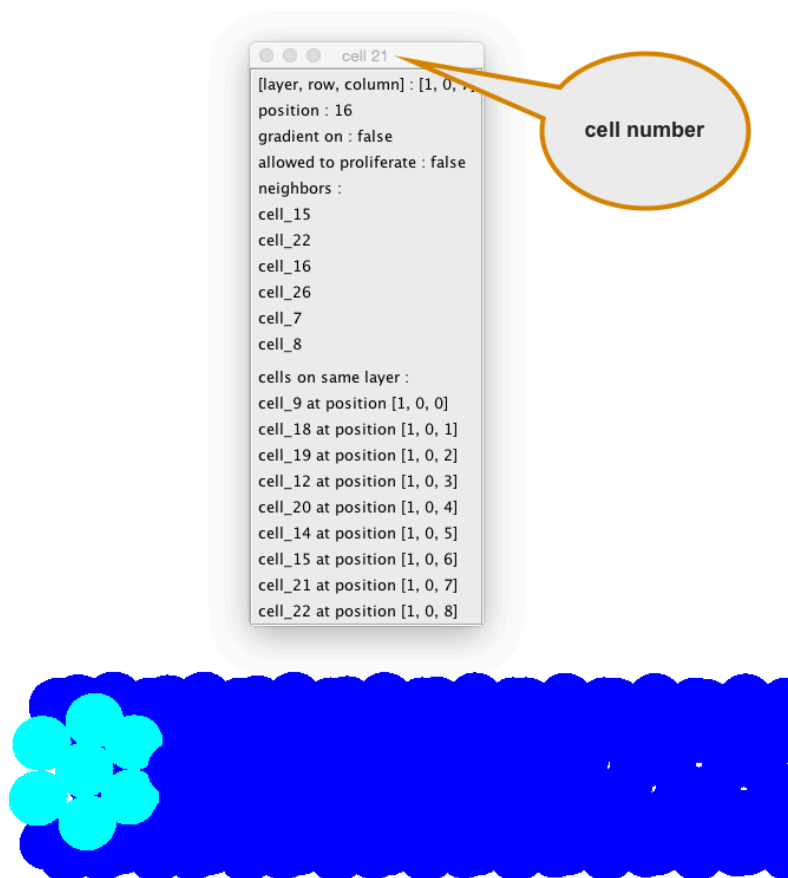
number of intermediate states during cell division



The '**plot cells**' field gives users the option to output the oscillators numerical data, which means that after each step of the *Runge-Kutta* method used to solve the system of differential equations modeling the GRN, the data will be written to a file, which can be either visualized by clicking the '**plot data**' button inside the application or be read by an appropriate program (like *gnuplot*) to visualize the time course of the concentrations.

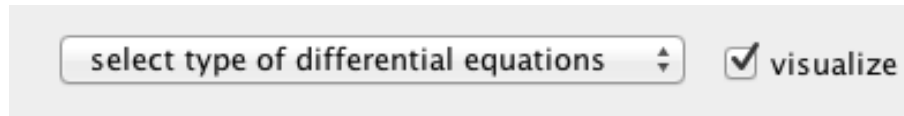


The cell number can be identified by clicking on the cell during simulation.



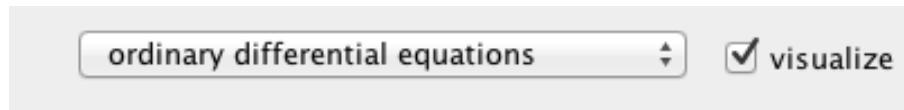
Before starting the simulation select the type of differential equations to model the GRNs.

- Start without any numerical differentiation, only cell visualization:



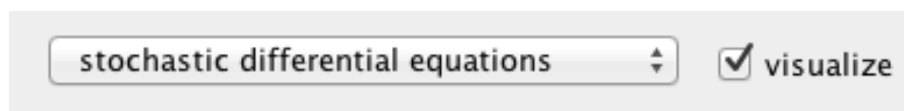
select type of differential equations ☒ visualize

- Modeling each cellular gene regulatory network by a system of ordinary differential equations:



ordinary differential equations ☒ visualize

- Modeling each cellular gene regulatory network by a system of stochastic differential equations:



stochastic differential equations ☒ visualize

As we use a simple 4th order *Runge-Kutta* Algorithm and most decay terms are linear (i.e. not saturated, we would otherwise introduce even more unknown constants) negative concentrations can be induced by choosing parameters or noise, which stray too wide from the standard values.

If negative values occur during the simulation a pop-up warning window informs the user about which cells (together with their neighbors) are involved, giving the opportunity to return and choose other parameter values or cancel the application.

By selecting the visualization of **Neurog3 mC** the current percentage of *Neurog3* positive cells will be written to the file *percent_of_ngn3_pos_cells.dat*, which can be found in the *SIM* directory. The file data can be visualized via *gnuplot*.

Implementation of the stochastic simulation

The stochastic differential equation system in each simulation cell extended from the following stochastic differential equation

$$\frac{dX_t}{dt} = f(X_t, t) \cdot dt + g(X_t, t) \cdot dW_t \text{ (see this [SDE tutorial](#))}$$

where

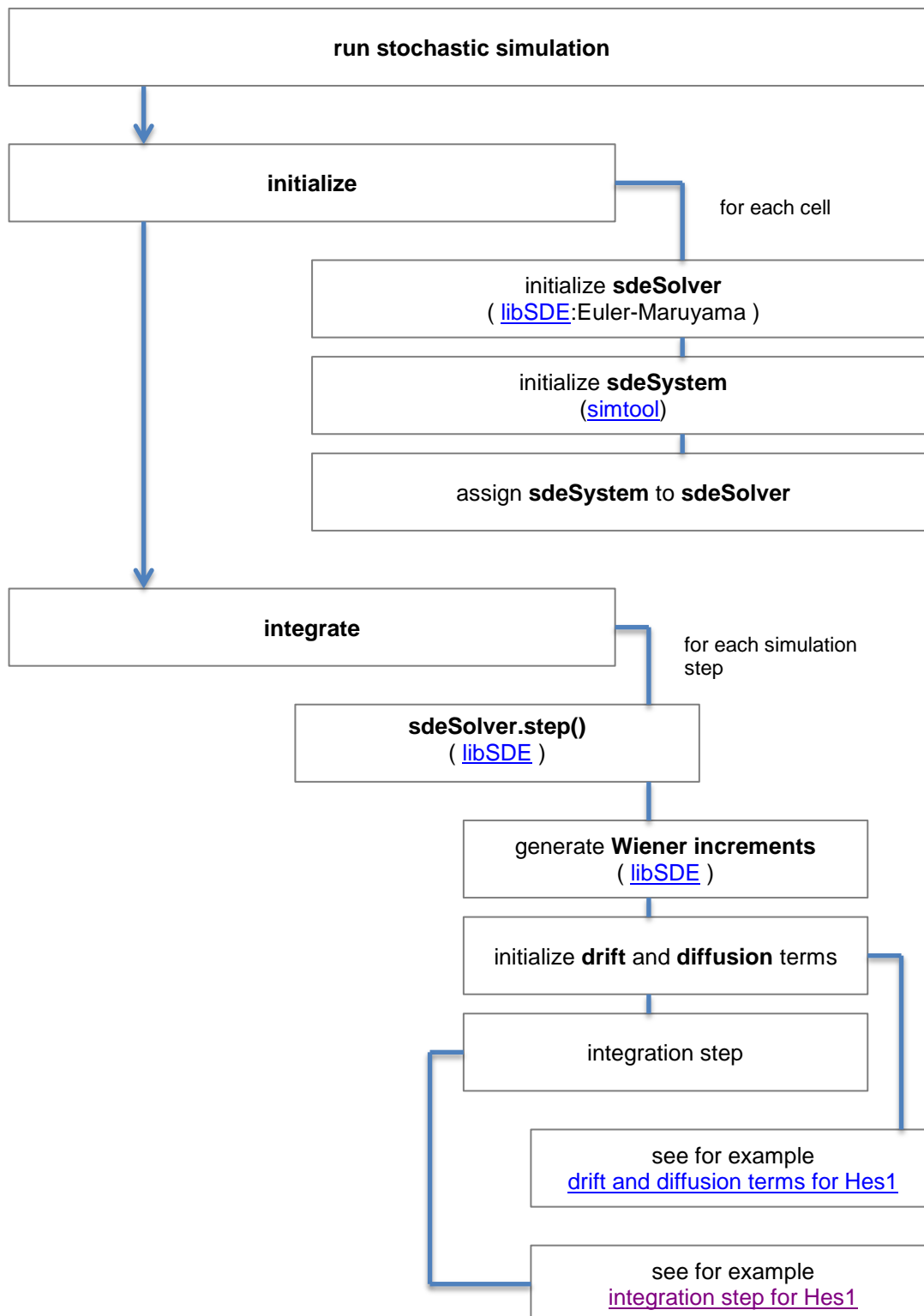
$X_t = X(t)$: random variable

$f(X_t, t)$: drift coefficient

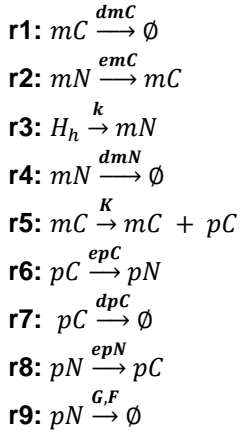
$g(X_t, t)$: diffusion coefficient

W_t : Wiener coefficient

has been solved by means of the Euler-Maruyama method based on the implementation provided by the [libSDE](#) Java library.



Reactions model for Hes1 (mC, mN, pC, pN)



legend: see manuscript 4.METHODOLOGY

Drift and diffusion terms for Hes1

drift term

$$F = \begin{pmatrix} -r1 + r2 \\ -r2 + r3 - r4 \\ r5 - r6 - r7 + r8 \\ r6 - r8 - r9 \end{pmatrix}$$

diffusion term

$$G = \begin{pmatrix} -\sqrt{r1} & \sqrt{r2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\sqrt{r2} & \sqrt{r3} & -\sqrt{r4} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sqrt{r5} & -\sqrt{r6} & -\sqrt{r7} & \sqrt{r8} & 0 \\ 0 & 0 & 0 & 0 & 0 & \sqrt{r6} & 0 & -\sqrt{r8} & -\sqrt{r9} \end{pmatrix}$$

Integration step for Hes1

dW - Wiener increments

$$dW = noise_strength \cdot \begin{pmatrix} rnd_1 \sqrt{t} \\ \vdots \\ rnd_9 \sqrt{t} \end{pmatrix}$$

rnd_i – random number generated with java *nextDouble()* method for reaction *i*

diffusion term

$$G_dW_term = \begin{pmatrix} -h\sqrt{r1}dW_1 + h\sqrt{r2}dW_2 \\ -h\sqrt{r2}dW_2 + h\sqrt{r3}dW_3 - h\sqrt{r4}dW_4 \\ h\sqrt{r5}dW_5 - h\sqrt{r6}dW_6 - h\sqrt{r7}dW_7 + h\sqrt{r8}dW_8 \\ h\sqrt{r6}dW_6 - h\sqrt{r8}dW_8 - h\sqrt{r9}dW_9 \end{pmatrix}$$

Euler Maruyama - step

$$\begin{pmatrix} mC \\ mN \\ pC \\ pN \end{pmatrix}_{t+1} = \begin{pmatrix} mC \\ mN \\ pC \\ pN \end{pmatrix}_t + h \cdot F + G_{dW_term}$$