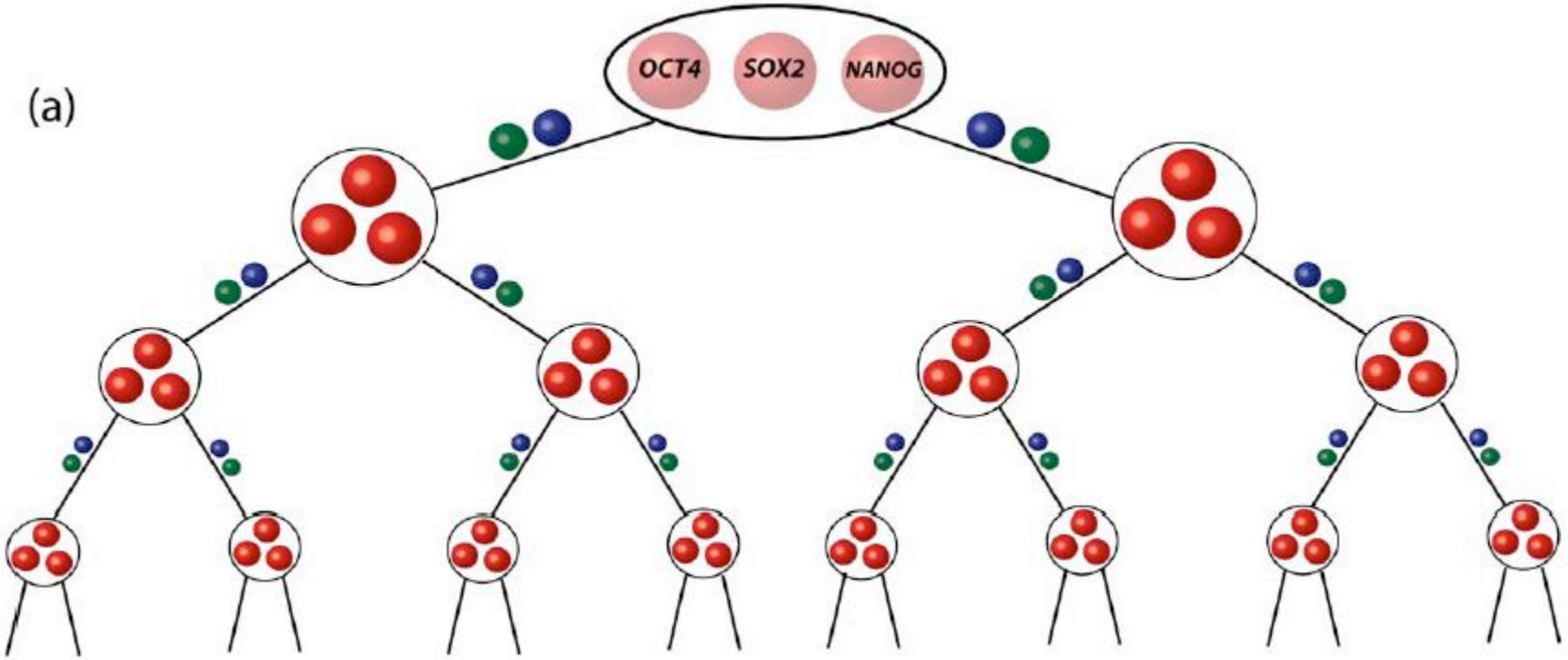
V8: Modelling the switching of cell fate

Aim : develop models for the architecture of coupled epigenetic and genetic networks which describe large changes in cellular identity (e.g., induction of pluripotency by reprogramming factors).



Artyomov et al., PLoS Comput Biol 6, e1000785 (2013)

Chronology of stem cell research

•1998 – embryonic stem cells

In 1998, James Thomson (US) isolated for the first time embryonic stem cells from surplus embryos „left over“ in fertilization clinics.

Since then, the research has progressed at an incredible speed.

Ethics „pro“:

ESC have the potential to grow replacement tissue for patients with diabetes, Parkinson or other diseases.

Ethics „contra“:

The technique requires destroying embryos. This has big ethical consequences.

In Germany, experimentation with humans is considered problematic due to the medical experiments pursued during the Nazi time.

Therefore, the above methods are forbidded by law in Germany!

Researchers are looking for new ways to generate stem cells without ethical problems.

Chronology of stem cell research

•2006 - Induced pluripotent stem cells (iPS)

The first solution was presented in August 2006 by the two Japanese Kazutoshi Takahashi and Shinya Yamanaka.

Using 4 control genes, they reprogrammed cells from mouse tail into a sort of embryonic state. The product was termed induced pluripotent stem cells (iPS cells).

Drawback: if used for medical treatment later, the inserted genes could enhance the risk of cancer.

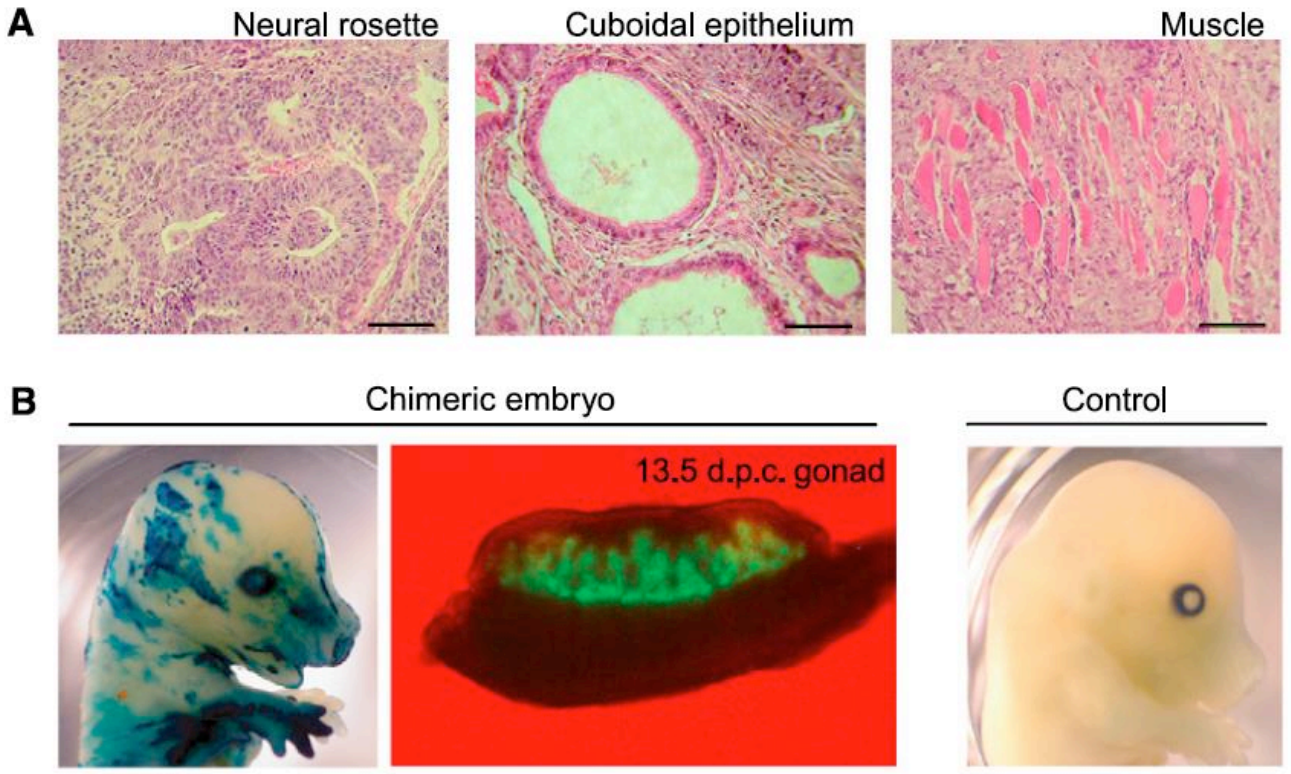
•2007 – human iPS cells

In 2007, similar success was managed with human skin cells.

Fewer and fewer control genes are necessary to generate iPS cells.

Spiegel Online

How can one show that iPS cells have stem cell potential?



Need to show that iPS cells implanted into an early embryo give rise to all 3 different types of tissue (endoderm, ektoderm, mesoderm).

Kim et al. Cell 136, 411 (2009)

Chronology of stem cell research

- **February 2009 – only one reprogramming gene required**

In February 2009, Hans Schöler presented iPS cells of mice that were reprogrammed from neural stem cells using only a single control gene.

- **March 2009 – Reprogramming gene removed**

Begin of March 2009: 2 teams of researchers present iPS cells that do not contain additional control genes in the genome.

Control genes were first inserted into the genome of human skin cells, and later removed.

- **March 2009 – Reprogramming gene not in genome**

End of March 2009: James Thomsom showed that control genes do not need to be inserted into the genome of the cells. He introduced an additional plasmid (ring genome) into the cell that was later removed.

Spiegel Online

Chronology of stem cell research

- **April 2009 – Reprogramming of mouse cells without genes**

Ende of April 2009: Sheng Ding (US) and others succeed to reprogram skin cells of mice into iPS without gene manipulations using proteins only.

This eliminates the risk of cancer due to insertion of genes.

- **May 2009 – Reprogramming of human cells without genes**

US-korean team around Robert Lanza manages to reprogram human cells into iPS cells using proteins (TFs) only.

ARTICLE

doi:10.1038/nature09591

Direct conversion of human fibroblasts to multilineage blood progenitors

Eva Szabo[1], Shravanti Rampalli[1], Ruth M. Risueño[1], Angelique Schnerch[1,2], Ryan Mitchell[1,2], Aline Fiebig-Comyn[1], Marilyne Levadoux-Martin[1] & Mickie Bhatia[1,2]

Characteristics of cell reprogramming

Generally: **reprogramming efficiency** is **very low** (few percent success rate).

Successful reprogramming may take very different times between days and weeks!

Cell reprogramming seems to be a stochastic process!

Modelling cell differentiation

OPEN ACCESS Freely available online

PLoS COMPUTATIONAL BIOLOGY

A Model for Genetic and Epigenetic Regulatory Networks Identifies Rare Pathways for Transcription Factor Induced Pluripotency

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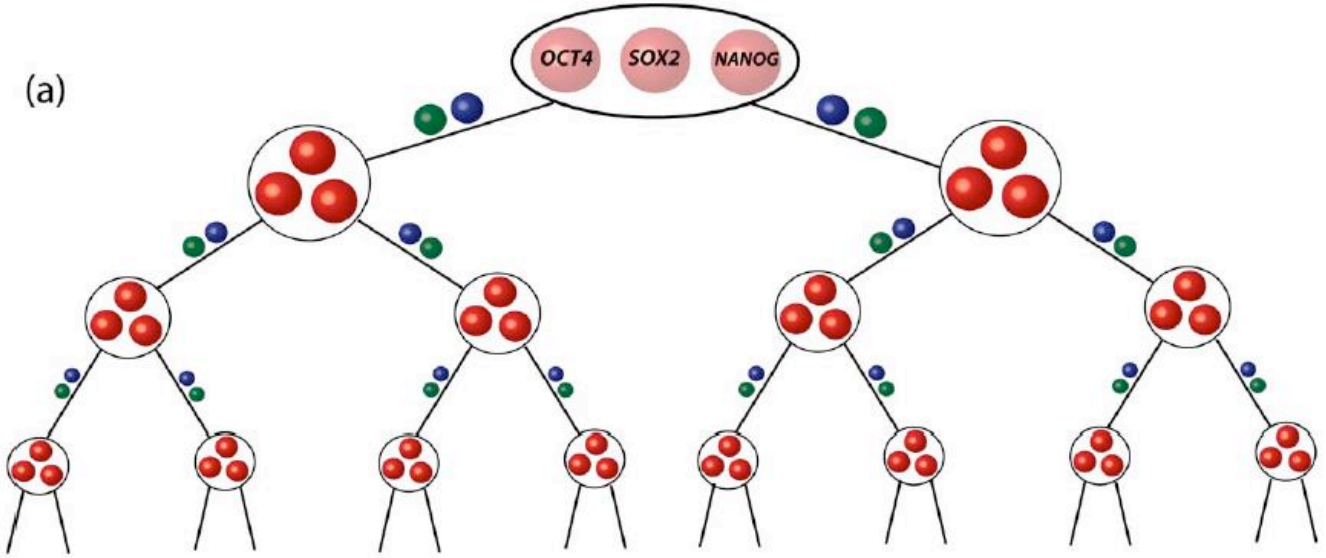
Consider only developmentally important genes.

Each set of genes responsible for maintenance of a particular cellular identity (e.g. Oct4, Sox2 for pluripotency) is described as a single module.

Arrange gene modules in a hierarchy.

For simplicity, from each cell state emanate two branches (Cayley tree).

Specification of genetic and epigenetic states that describe cellular states



Only the master-regulatory genes that govern cell state are arranged in a hierarchy (house keeping, stress-response and many other genes are not considered).

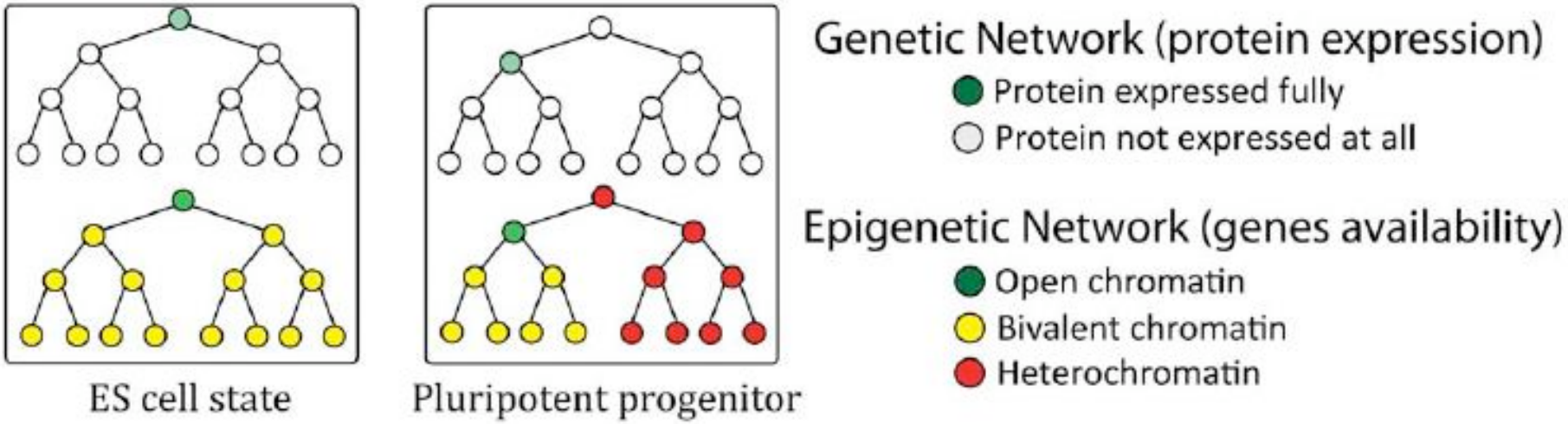
Each node of the hierarchy represents an ensemble of master-regulatory genes that govern a particular cellular state. E.g. genes in the top node are known master regulators of the embryonic stem cell state (e.g. Oct4, Sox2, Nanog).

When a cell is in the ES state, only these 3 genes will be expressed while other genes will not.

Similarly, when a cell is fully differentiated, genes in one of the bottom modules will be expressed but not any other gene in the network.

Artyomov et al., PLoS Comput Biol 6, e1000785 (2013)

Separate Genetic and Epigenetic Networks



Cellular identity is determined by both epigenetic (chromatin marks, DNA methylation) and genetic (expression profile) states.

Shown are examples of two states (ES state and "left" pluripotent progenitor).

2 lattices are needed to describe the state of gene expression and the epigenome:
the top lattice reflects the expression levels of master-regulatory proteins in the ES/progenitor state and the bottom lattice reflects the epigenetic state of master-regulatory genes in the ES/progenitor state.

Artyomov et al., PLoS Comput Biol 6, e1000785 (2013)

Ising model

The **Ising model** named after the physicist Ernst Ising, is a mathematical model of **ferromagnetism** in statistical mechanics.

The model consists of discrete variables that represent magnetic dipole moments of atomic **spins** that can be in one of two states (+1 or −1).

The spins are arranged in a graph, usually, a lattice, allowing each spin to interact with its neighbors.

The model allows the identification of **phase transitions**, as a simplified model of reality.

The two-dimensional square-lattice Ising model is one of the simplest statistical models to show a phase transition.

Ising model

Consider a set of lattice sites Λ, each with a set of adjacent sites forming a lattice.

For each lattice site $j \in \Lambda$ there is a discrete variable $\sigma_j \in \{+1, -1\}$.
A **spin configuration** $\sigma = (\sigma_j)_{j \in \Lambda}$ is an assignment of spin valuse to each lattice site.

For any two adjacent sites $i, j \in \Lambda$ one has an **interaction** J_{ij}, and a site $i \in \Lambda$ has an **external magnetic field** h_i.
The **energy** of a configuration σ is given by the Hamiltonian Function

$$H(\sigma) = -\sum_{<i\ j>} J_{ij}\sigma_i\sigma_j - \mu \sum_j h_j \sigma_j$$

where the first sum is over pairs of adjacent spins.
<*ij*> indicates that sites *i* and *j* are nearest neighbors.
μ is the magnetic moment of a spin that interacts with the magnetic field.

The parallel arrangement of spins is energetically preferred. Rearrangements arise from thermal fluctuations.
Solve analytically or by Monte-Carlo simulations.

Review (Comput Chemistry): Metropolis Algorithm

The most often used technique to select conformers by Monte-Carlo methods („importance sampling“) is the **Metropolis Algorithm**:

(1) construct starting configuration of molecule

(2) perform random change of degree of freedom (e.g. torsion angle or spin flip)

(3) compute change in energy ΔE due to conformation change.

(4) if $\Delta E < 0$ accept new configuration

if $\Delta E > 0$ compute probability $W = \exp\left(-\frac{\Delta E}{k_B T}\right)$

generate random number **r** $\in$ [0,1]

accept new configuration if w $\geq$ **r**, otherwise reject.

Because Boltzmann-weighted energy difference is compared to a random number, sometimes **high-energy** conformers get accepted.

This yields an **ensemble** of conformations with an energy distribution according to a **Boltzmann distribution**.

Adaptation of Ising model to switching of cell fate

Define an **epigenetic lattice** where a discrete epigenetic state is associated with each node (-1,0,+1).

S^{epigen} = -1 corresponds to closed chromatin,
S^{epigen} = 0 : bivalent chromatin and
S^{epigen} = +1 : open chromatin.

The **genetic lattice** describes expression of proteins from master-regulatory modules.

It has discrete gene expression states associated with each node (0, +1).

S^{gen} = 0 : absence of any protein expression from the given gene,
S^{gen} =+1 : maximum protein expression from the gene.

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“Epigenetic energy function” of cell fate

$$H[\{S_i^{ep}\}] = -G\sum_i <S_i^{gen}> S_i^{ep}$$
$$+G \sum_{i,j \in sibling,progeny\ of\ i} <S_j^{gen}> S_i^{ep}$$
$$+G \sum_{i,j \in parent\ of\ i} <S_j^{gen}> |S_i^{ep}|$$
$$+H \sum_{\substack{j,i \notin progeny\ of\ j \\ and\ i \neq j}} (<S_j^{gen}> - a) S_i^{ep}$$

S_i^{ep} : epigenetic spin state of i-th module,
S_i^{gen} : protein expression level of i-th module.

Angular brackets : average expression level of j-th module obtained during the preceding interphase, and could include protein products of ectopic genes or signaling events.

$|S_i^{ep}|$: absolute value of S_i^{ep} .

G > 0 : parameter that represents the strength with which the protein atmosphere can modify the epigenetic state by altering histone marks.
H > 0 : parameter that represents the strength of the DNA methylation constraint.
a > 0 : constant that favors values of $S_i^{ep} < a$ if proteins expressed by gene *j* are present.

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"Genetic energy function" of cell fate

$$H[\{S_i^{gen}\}] = -F \sum_i (<S_i^{ep}> - b) S_i^{gen}$$

$$+ J \sum_{i \neq j \in nearest\ neighbors} S_i^{gen} S_j^{gen}$$

Angular brackets : average value of epigenetic state of the i-th module obtained during the preceding telophase.

F > 0: constant that represents how strongly a protein is expressed or repressed if it is in open chromatin state or in heterochromatin, respectively.

b > 0 : constant; protein expression is favored if $<S_i^{ep}>$ > b.

The form of the first term implies that protein expression is more strongly repressed if a gene is packaged in heterochromatin compared to if it is bivalently marked.

J represents the strength of mutual repression by other proteins.

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Monte Carlo simulation of cell fate

As in the standard Monte-Carlo algorithm, the lattice spins (+1/0/-1 on the epigenetic lattice; +1/0 on the genetic lattice) are **initialized randomly**.

The Monte-Carlo **move** consists of
1) randomly choosing a node on the lattice;

2) randomly deciding on the choice of a new value of S_i for this node
(i.e. if S_i^{epigen} was 0 then it can become -1 or +1 with equal probability);

3) the energy for this configuration is computed according to the appropriate Hamiltonian (energy function);

4) attempted changes in state are accepted with probability equal to
$\min [1, \exp \{-\beta \Delta H(S_i)\}$.

The parameter β is analogous to the inverse temperature 1/kT used in simulation of thermal systems, and sets the scale for the parameters, F, G, H and J.

Run enough MC steps in each phase until running averages of S^{gen} /S^{epigen} converge.

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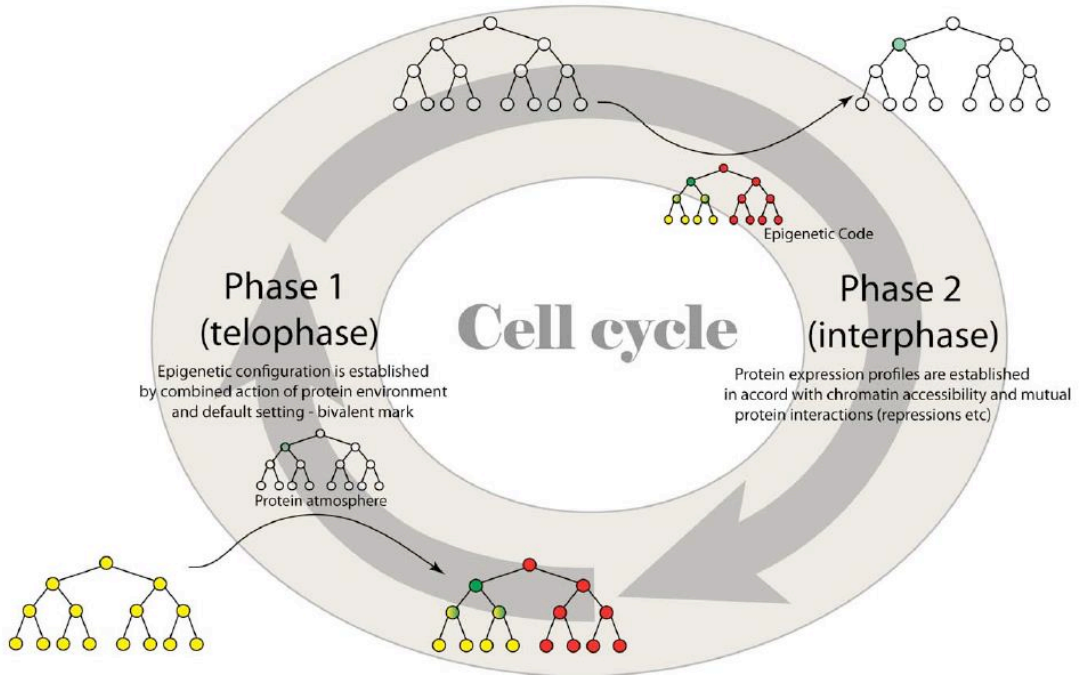
Simplified model for progression through cell cycle



For simplicity, the cell cycle is divided into two generalized phases, interphase and telophase.

Gene expression occurs during the **interphase**, while cell division and associated processes occur in the telophase.

In the interphase gene expression profile is governed by the stable epigenetic marks on the master-regulatory genes.

In the **telophase**, however, protein environment can change the **epigenetic marks** of the master-regulatory genes.

Differentiation signals (newly expressed proteins) determine future epigenetic marks created during telophase due to the action of the new protein environment.

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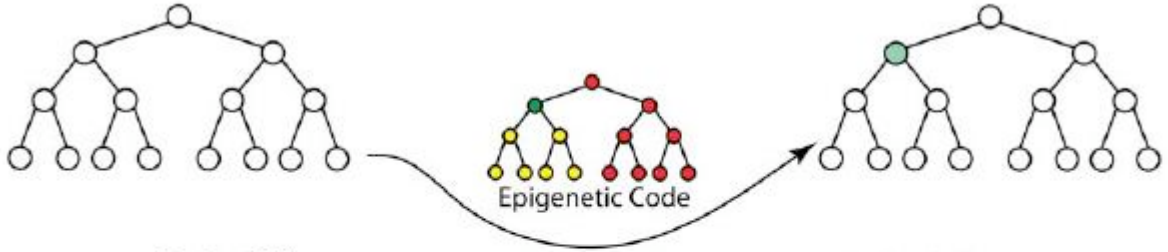
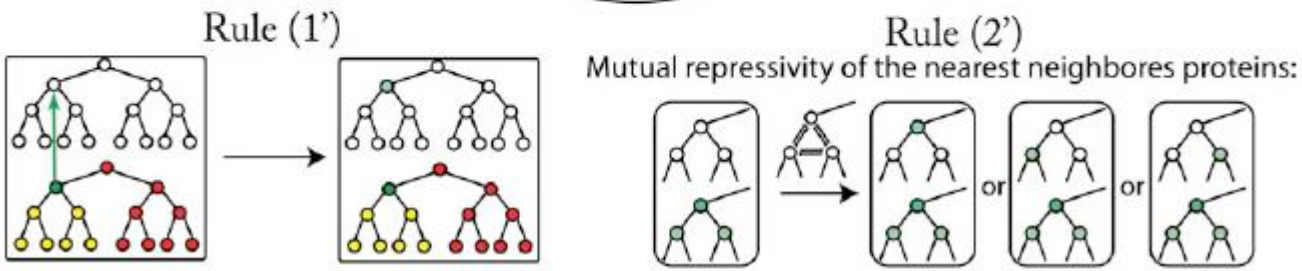
Transcriptional dynamics during interphase



Rules that govern inter-actions within epigenetic and genetic networks.



During interphase, gene expression profiles of master regulatory modules are established.

Gene expression is influenced by epigenetic marking of the corresponding gene and interactions between expressed proteins. 2 rules reflect this in our simulation:

1) When a master-regulatory gene is epigenetically marked positively, it favors expression of the corresponding protein;

2) when 2 (or 3) neighboring genes are in epigenetically open states, they all favor expression of corresponding proteins, but due to their mutually repressive action only one of 2 (or 3) genes are expressed. Which gene is expressed is chosen stochastically.

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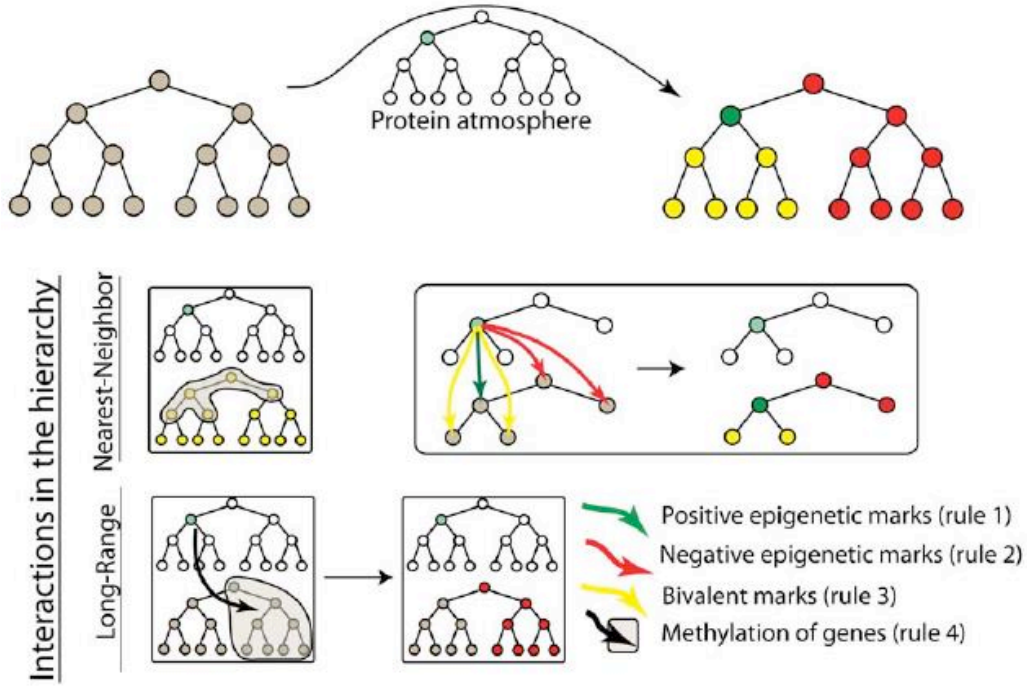
Epigenetic dynamics during telophase



During the telophase, the protein environment can alter the epigenetic marks on the master-regulatory genes.

Epigenetic marks on both neighboring and distant genes in the hierarchy can be altered.

Long-range effect is typically mediated through DNA methylation which epigenetically silences all of the master-regulatory genes of unrelated lineages and also ancestral states.

Short-range interactions affect nearest-neighbors differentially: progenies of master-regulatory genes are preferentially put into bivalent states while progenitor and competing lineage modules are epigenetically silenced.

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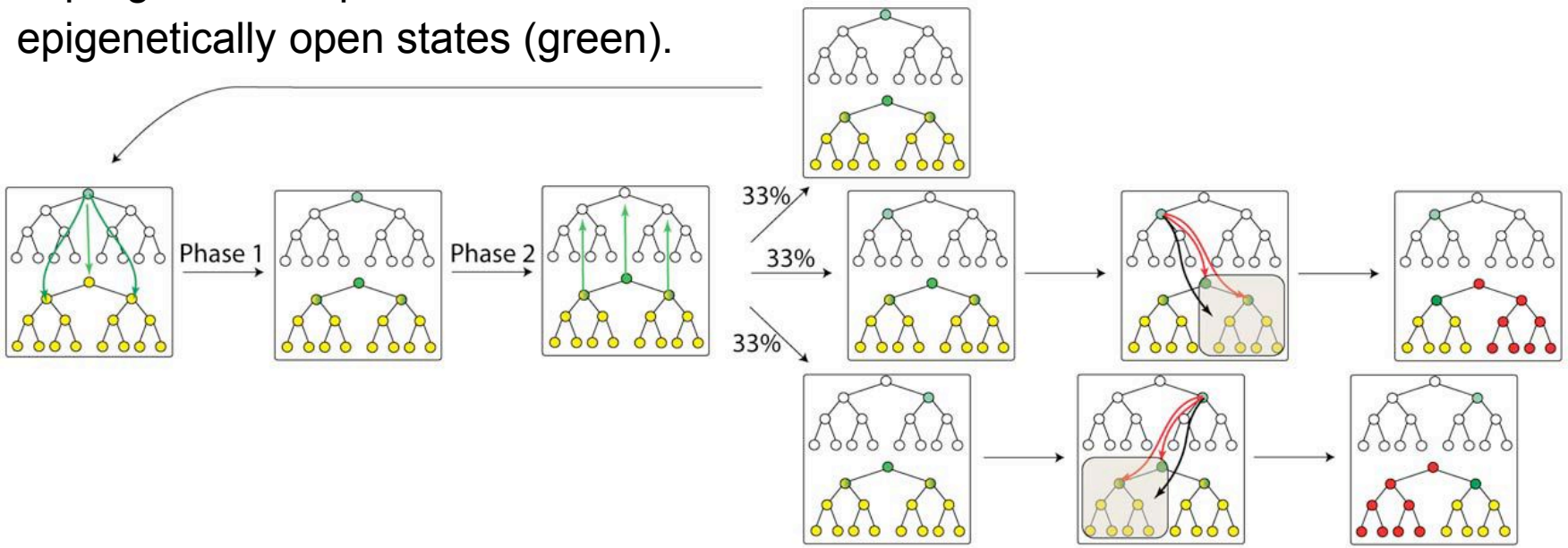
Changing cellular identity during self-initiated differentiation of the ES cell-state

Phase 1: Process begins with cell division where regulatory modules of progenies are put into epigenetically open states (green).



In phase 2 only one of the 3 neighboring proteins can be actually expressed. Thus, one of 3 possibilities is realized: self-renewal, and differentiation to the "left" or "right" lineages. In the absence of external stimuli, in our simulations, there is an equal chance to observe each outcome.

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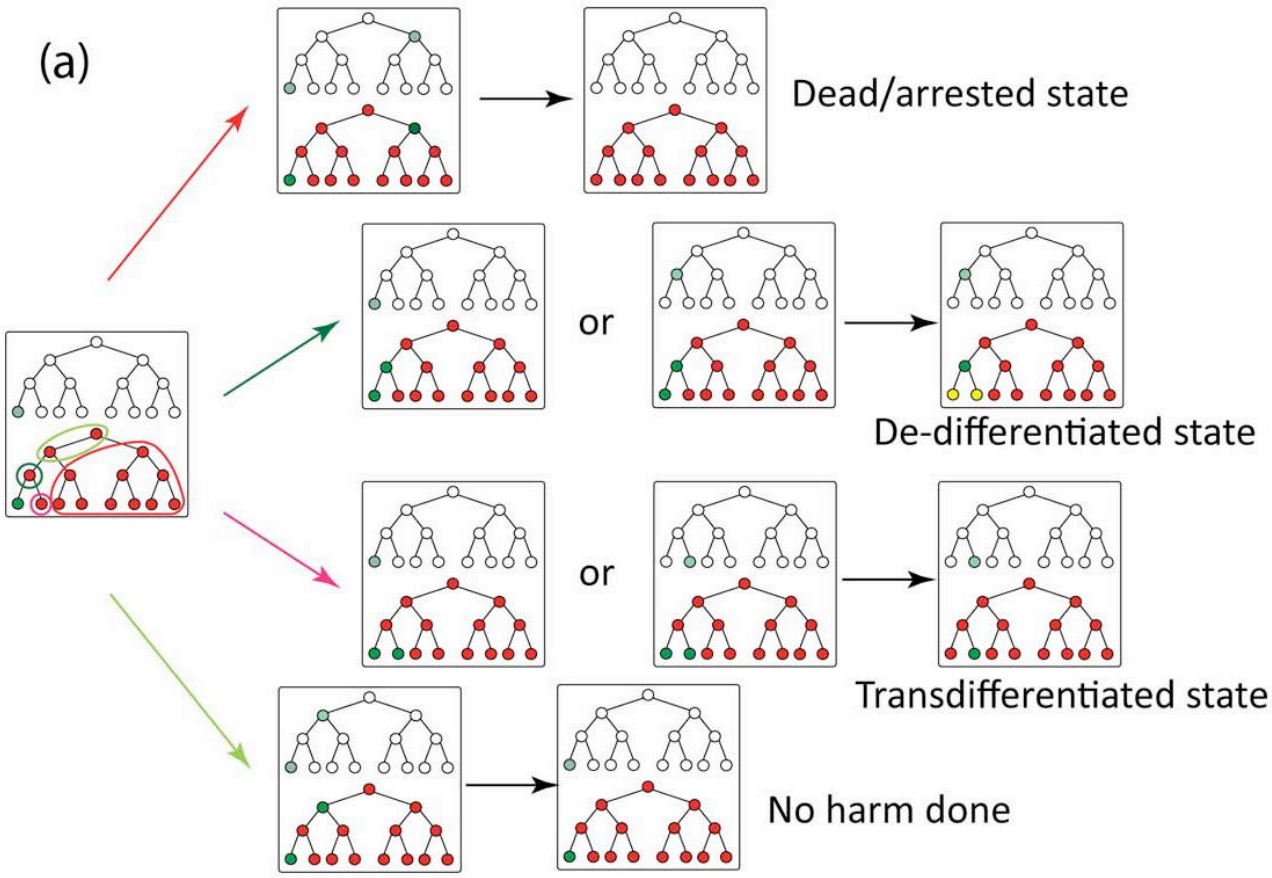
Reprogramming may result from random epigenetic changes



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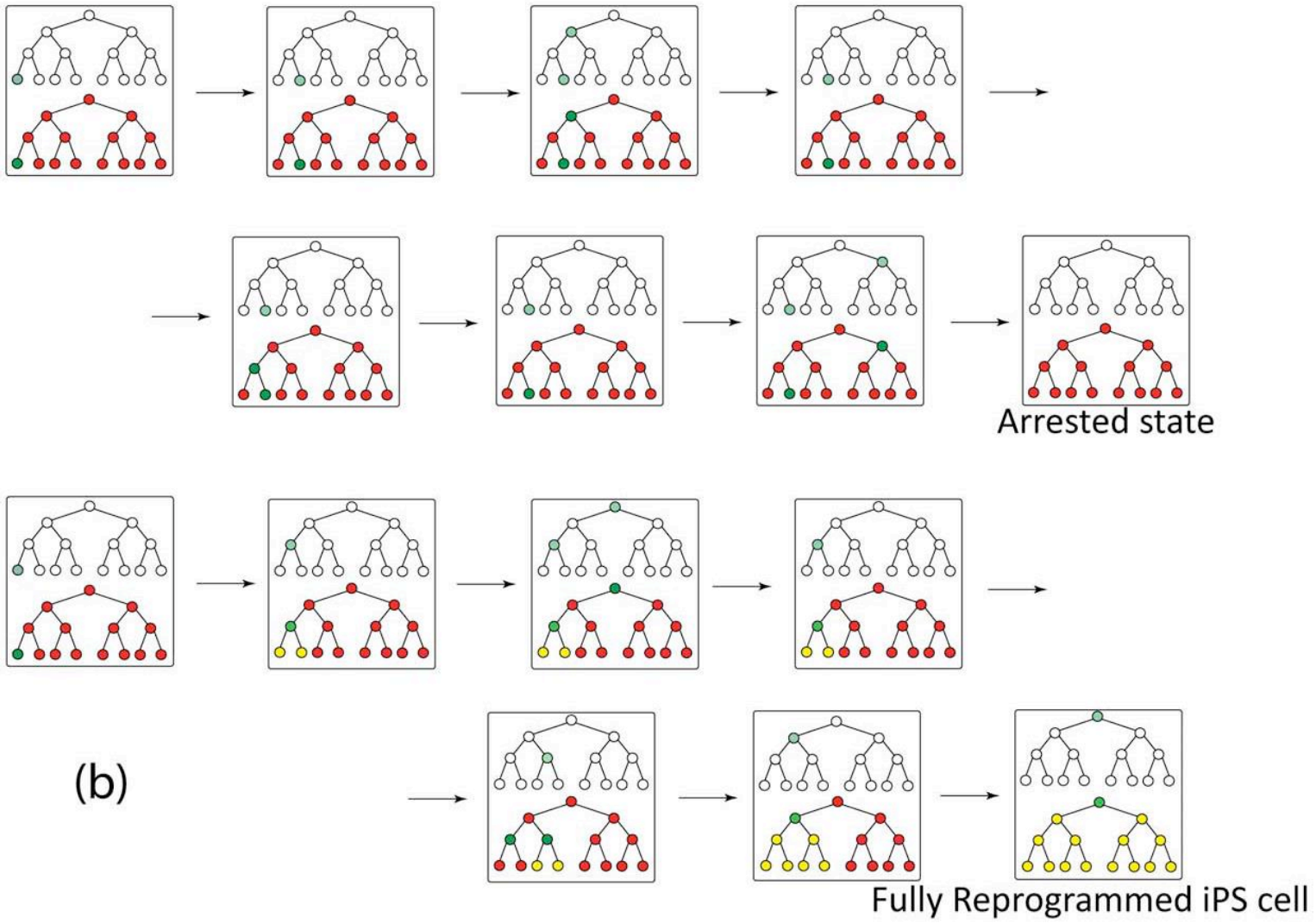
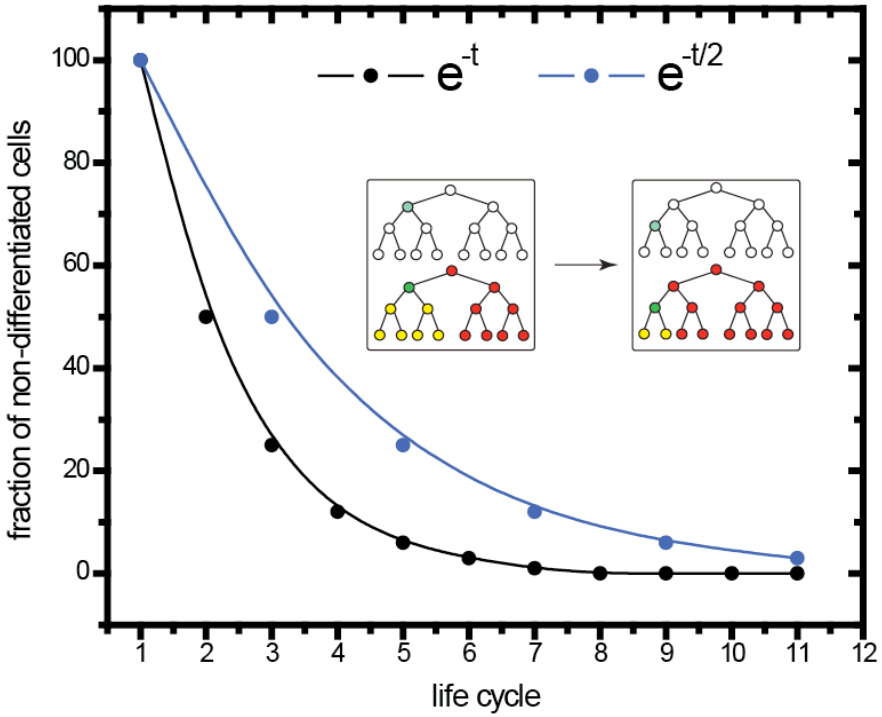
2 real simulations



Artyomov et al., PLoS Comput Biol 6, e1000785 (2013)

Dynamics of cell differentiation



Dynamics of cell differentiation upon receiving cues (input signals) of different strength.

The simulations show that the progenitor cells differentiate in accord with first order kinetics, with the lifetime of progenitor cells depending on the signal strength.

The blue curve describes the behavior of a cell population which received a signal that is twice as weak as the population represented by the black line.

Artyomov et al., PLoS Comput Biol 6, e1000785 (2013)

Alternative modeling approach – more gene details

frontiers in PHYSIOLOGY

ORIGINAL RESEARCH ARTICLE
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A stochastic model of epigenetic dynamics in somatic cell reprogramming

Max Flöttmann, Till Scharp and Edda Klipp*

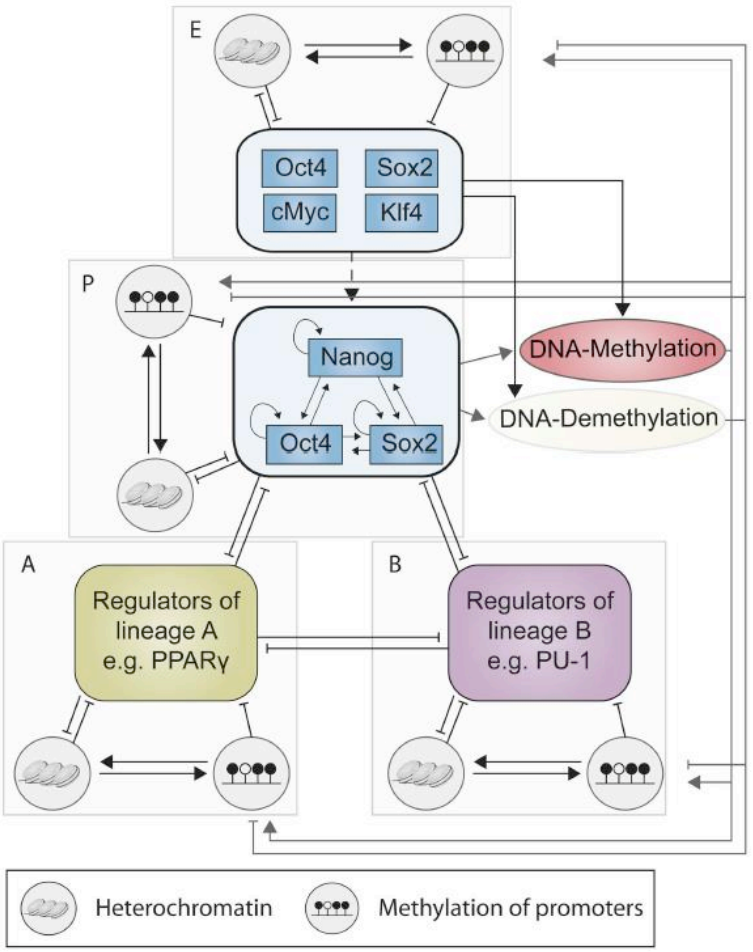
Department of Biology, Theoretical Biophysics, Humboldt-Universität zu Berlin, Berlin, Germany

Aims also at building an abstract model of combined networks that govern pluripotency and reprogramming.

Boolean model used where a cell state is defined as a simple binary vector of the states of all variables.

Flöttmann et al., Frontiers Physiol 3, 216 (2012)

General model structure



Transcriptional regulators that account for the activation of a certain cell state are combined into a module.

Full model contains 4 modules:
- 2 different differentiation modules *A* and *B*,
- the pluripotency module *P*, and
- the exogenous reprogramming genes *E*.

Each module is governed by the activity of the other modules as well as its epigenetic states

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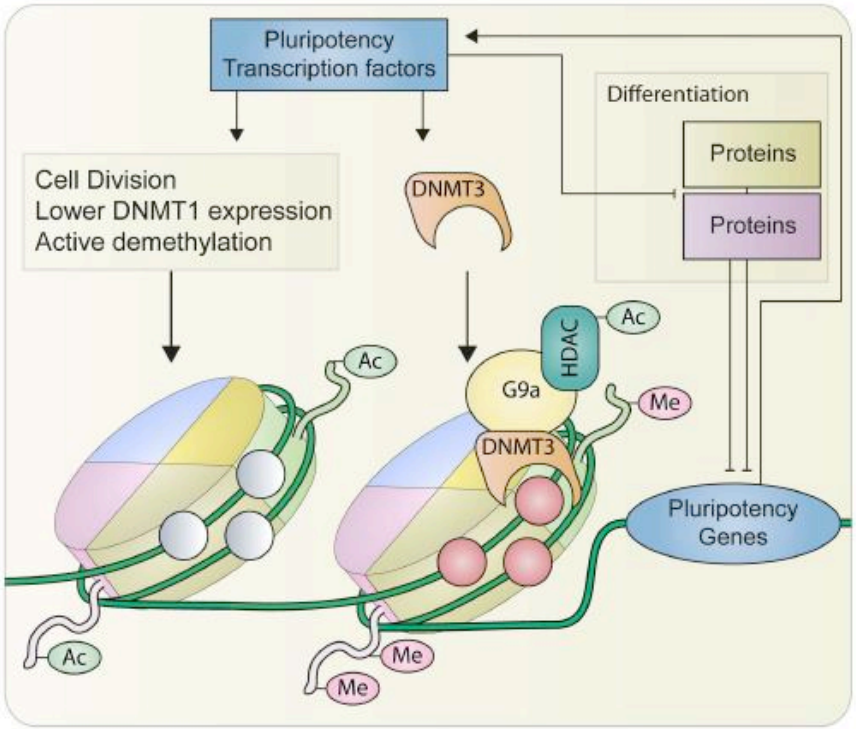
Processes described by model



On the other hand activation of pluripotency genes also leads to a higher cell division rate,a suppression of methylation maintenance and probably active demethylation, which also increases the chances of euchromatin formation

Model describes connections between DNA methylation, histone modifications and the pluripotency master regulators.

Pluripotency TFs activate their own expression and can be suppressed by factors regulating differentiation.

The pluripotency factors themselves increase the expression of *DNMT3* which enables *de novo* methylation of DNA preferably in combination with repressive histone modifications such as methylation or deacetylation (right nucleosome).

Flöttmann et al.,
Frontiers Physiol 3,
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Boolean Networks

Boolean networks limit the state of a gene to either ON or OFF and describe connections between the genes by using logical operators,
e.g., AND, OR, NOT (generally written as $\wedge$, $\vee$, and $\neg$).

E.g. if two transcription factors A and B are needed to activate gene C
this would translate to the logical function

$$C(t + 1) = A(t) \wedge B(t)$$

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Boolean Networks

In formal terms, a Boolean network can be represented as a graph G = (V, E) consisting of a set of *n* nodes V = {v_1, …, v_n} and a set of *k* edges E = {e_1, …, e_n} between the nodes.

For every time point *t*, each node v_i has a state $v_i(t) \in \{0, 1\}$ denoting either no expression or expression of a gene or absence or presence of activity of a regulatory property, respectively.

In a non-probabilistic Boolean network, the state vector, or simply the state **S**(**t**) of the network at time *t* corresponds to the vector of the node states at time *t*, i.e., $\mathbf{S}(\mathbf{t}) = (v_1(t), \ldots, v_n(t))$.

Thus, since every $v_i(t)$ can take only 2 possible values 0 or 1, the number of all possible states is 2^n .

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Probabilistic Boolean Networks

In probabilistic Boolean networks (PBNs), we are dealing with a **probability distribution** over several states at each time point.

This is why, in order to extend the definition of states to probabilistic Boolean Networks, we will refer to a specific state as $\mathbf{S_i}$ from now on where $i \in \{0, \ldots, 2^n\}$, independent of the time of its appearance.

Every node is updated at every time point by application of a set of update functions $F = \{F_1, \ldots, F_n\}$ that integrate the input information of edges on one node.

In other words, the function F_i assigns a new state value to the node v_i at time $t + 1$, i.e., $v_i(t + 1)$.

They depend on the state of k input nodes with $k \in \{0, \ldots, n\}$ at time t.

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Probabilistic Boolean Networks

Example: let us assume that there is experimental data showing that both transcription factors A and B activate gene C, but it is unclear whether they can act separately or only in combination

Then, there are several logical function that can describe the interaction of A,B, C.

In probabilistic Boolean networks this **uncertainty** is taken into account by relaxing the constraint of fixed update rules F_i and by permitting instead one or more functions per node.

Thus, function F_i is replaced by a set of functions $F_i = \{ f^i_j \}$ with $j \in \{1, \ldots, l(i)\}$, where f^i_j is a Boolean logic function and
$l(i)$ the total number of functions for node v_i .

In each update step the functions are chosen randomly according to their probability (which we assign).

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Probabilistic Boolean Networks

The PBN can be viewed as an ensemble of *N* standard Boolean networks, where

$$N = \prod_{i=1}^{n} l(i)$$

In each simulation step, we choose one of the networks to update the state.

The probability of each network being chosen is the product of the probabilities of the chosen functions.

The vector $\mathbf{D}^{t} = (D^{t}_{1}, \ldots, D^{t}_{n})$ now comprises the probabilities of all $r = 2^{n}$ states at time *t*, i.e.,the probability of the network to be in this state.

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Probabilistic Boolean Networks

Simulations performed using R-package BoolNet (Müssel et al. 2010)

Model contains 14 variables

Thus, there are 2^{14} = 16,384 possible states.

Table 1 | Variables and states of our model.

	m_e^E	m_m^E	m_{hc}^E	m_e^P	m_m^P	m_{hc}^P	m_e^A	m_m^A	m_{hc}^A	m_e^B	m_m^B	m_{hc}^B	*dnmt*	*demeth*
Pluripotent state $\mathbf{S}_1$	0	1	1	1	0	0	0	1	1	0	1	1	1	1
Differentiated state $\mathbf{S}_2$	0	1	1	0	1	1	1	0	0	0	1	1	0	0
Differentiated state $\mathbf{S}_3$	0	1	1	0	1	1	0	1	1	1	0	0	0	0
Weight vector $\mathbf{W}_1$	0.5	0.5	0.5	2.0	10.0	5.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0
Weight vector $\mathbf{W}_1$	0.5	0.5	0.5	2.0	2.0	2.0	2.0	10.0	5.0	2.0	2.0	2.0	1.0	1.0
Weight vector $\mathbf{W}_1$	0.5	0.5	0.5	2.0	2.0	2.0	2.0	2.0	2.0	2.0	10.0	5.0	1.0	1.0

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Probabilistic Boolean Networks

We can define a $(2^n \times 2^n)$ matrix **A**, that contains the probability to transition from state *i* to state *j* given all possible networks.

If there is no network allowing the transition $i \rightarrow j$, $A_{ij} = 0$ otherwise A_{ij} is the sum of the probabilities of all the networks allowing this transition.

Matrix **A** is a state transition matrix of a homogeneous Markov process.

Thus, given a (1×2^n) vector $\mathbf{D^0}$ with a start probability for each state we can recursively simulate the system from *t* to *t* + 1 (eq. (1)) or as well directly deduce the value at *t* + 1 of this geometric progression (eq. (2))

$$\mathbf{D}^{t+1} = \mathbf{D}^t \cdot \mathbf{A} \qquad (1)$$

$$\mathbf{D}^{t+1} = \mathbf{D}^0 \cdot \mathbf{A}^{t+1} \qquad (2)$$

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The epigenetic landscape

A module consists of 3 nodes,

- an expression node

- a DNA methylation node

- and a chromatin structure node

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216 (2012)

4 update functions for methylation of pluripotency genes

$$m_m^A(t+1) = m_m^A(t) \vee dnmt(t) \wedge m_{hc}^A$$
$$m_m^A(t+1) = m_m^A(t) \wedge \left(demeth(t) \vee m_{hc}^A\right)$$
$$m_m^A(t+1) = m_m^A(t) \wedge demeth(t)$$
$$m_m^A(t+1) = m_m^A(t)$$

$m^A{}_m$ and $m^A{}_{hc}$: methylation and chromatin states of module *A*, respectively.

dnmt: presence of de novo DNA methyltransferase DNMT3A/B

demeth: combines all processes leading to demethylation of DNA

Similar rules hold for modules *B* and P.

Note that probabilities of the formulas sum up to 1.

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Update functions for chromatin changes

Chromatin changes are dependent on the expression of the module‘s genes.

$$m_{hc}^{A}(t+1) = m_{hc}^{A}(t) \vee m_{m}^{A}(t) \wedge \neg m_{e}^{A}(t)$$
$$m_{hc}^{A}(t+1) = m_{hc}^{A}(t) \vee \neg m_{e}^{A}(t)$$
$$m_{hc}^{A}(t+1) = m_{hc}^{A}(t) \wedge \neg m_{m}^{A}(t)$$
$$m_{hc}^{A}(t+1) = m_{hc}^{A}(t)$$

m^A_e *:* expression of module *A*

m^A_{hc} : chromatin states of module *A*.

m^A_m *:* DNA methylation of module *A*

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Update functions for gene expression

The expression of a module is controlled by its epigenetic states.

$$m_e^A(t+1) = m_e^A(t) \wedge \neg\left(m_e^B \vee m_e^P(t)\right) \wedge \neg m_m^A(t)$$

$$m_e^A(t+1) = m_e^A(t) \wedge \neg\left(m_e^B \vee m_e^P(t)\right) \wedge \neg m_{hc}^A(t)$$

m^A_e *:* expression of module *A*

m^A_{hc} : chromatin states of module *A*.

m^A_m *:* DNA methylation of module *A*

If both epigenetic submodules are inactive (hc and meth), the expression of the genes in the next time step depends only on the transcription factors.

Some further rules left out …

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Relation between 14 state variables and cell states

Table 1 | Variables and states of our model.

	m_o^E	m_m^E	m_{hc}^E	m_o^P	m_m^P	m_{hc}^P	m_o^A	m_m^A	m_{hc}^A	m_o^B	m_m^B	m_{hc}^B	*dnmt*	*demeth*
Pluripotent state $\mathbf{S}_1$	0	1	1	1	0	0	0	1	1	0	1	1	1	1
Differentiated state $\mathbf{S}_2$	0	1	1	0	1	1	1	0	0	0	1	1	0	0
Differentiated state $\mathbf{S}_3$	0	1	1	0	1	1	0	1	1	1	0	0	0	0
Weight vector $\mathbf{W}_1$	0.5	0.5	0.5	2.0	10.0	5.0	2.0	2.0	2.0	2.0	2.0	2.0	1.0	1.0
Weight vector $\mathbf{W}_1$	0.5	0.5	0.5	2.0	2.0	2.0	2.0	10.0	5.0	2.0	2.0	2.0	1.0	1.0
Weight vector $\mathbf{W}_1$	0.5	0.5	0.5	2.0	2.0	2.0	2.0	2.0	2.0	2.0	10.0	5.0	1.0	1.0

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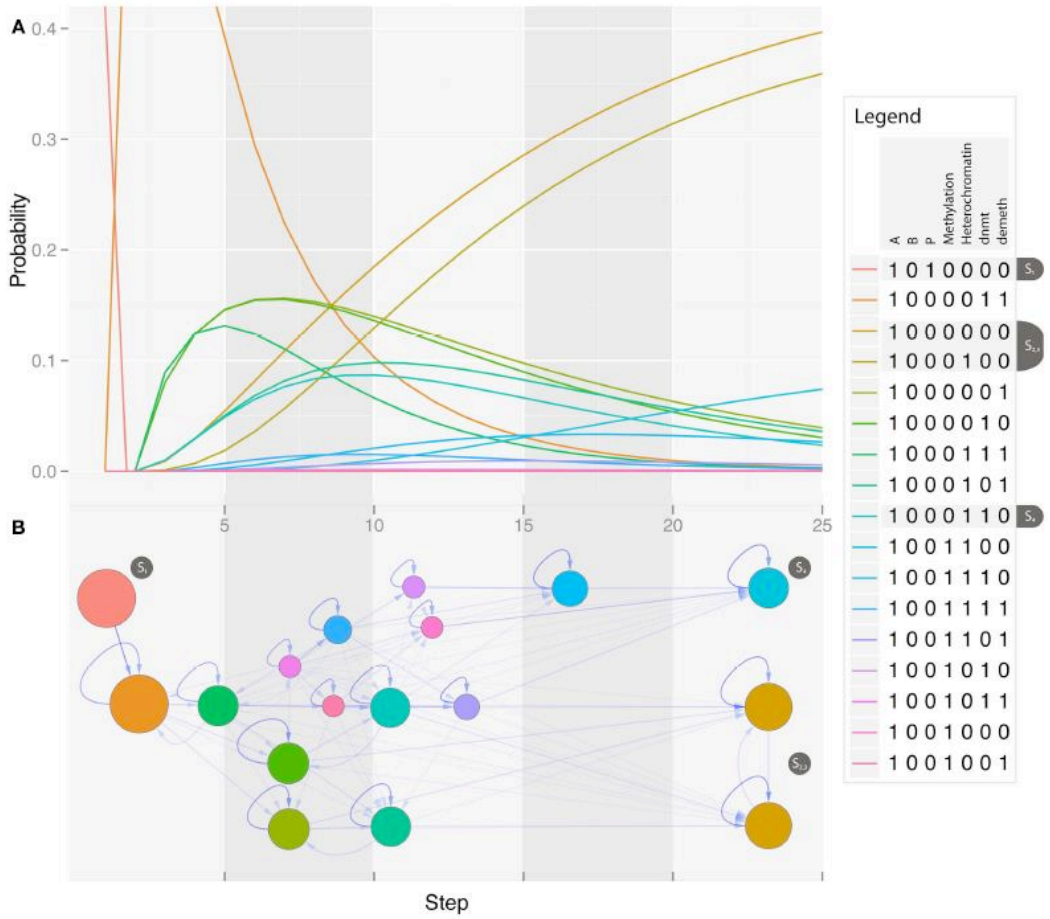
Dynamics of isolated pluripotency module



Dynamics (A) and state space (B) of the pluripotency module during overexpression of differentiation factors.

The network quickly leaves the pluripotent state and passes across a number of transient states into two different attractors. The node in blue (lower right) is a point attractor in the completely differentiated state and the nodes in brown are part of a cyclic attractor consisting of the unmethylated state in either a euchromatin or heterochromatin structure.

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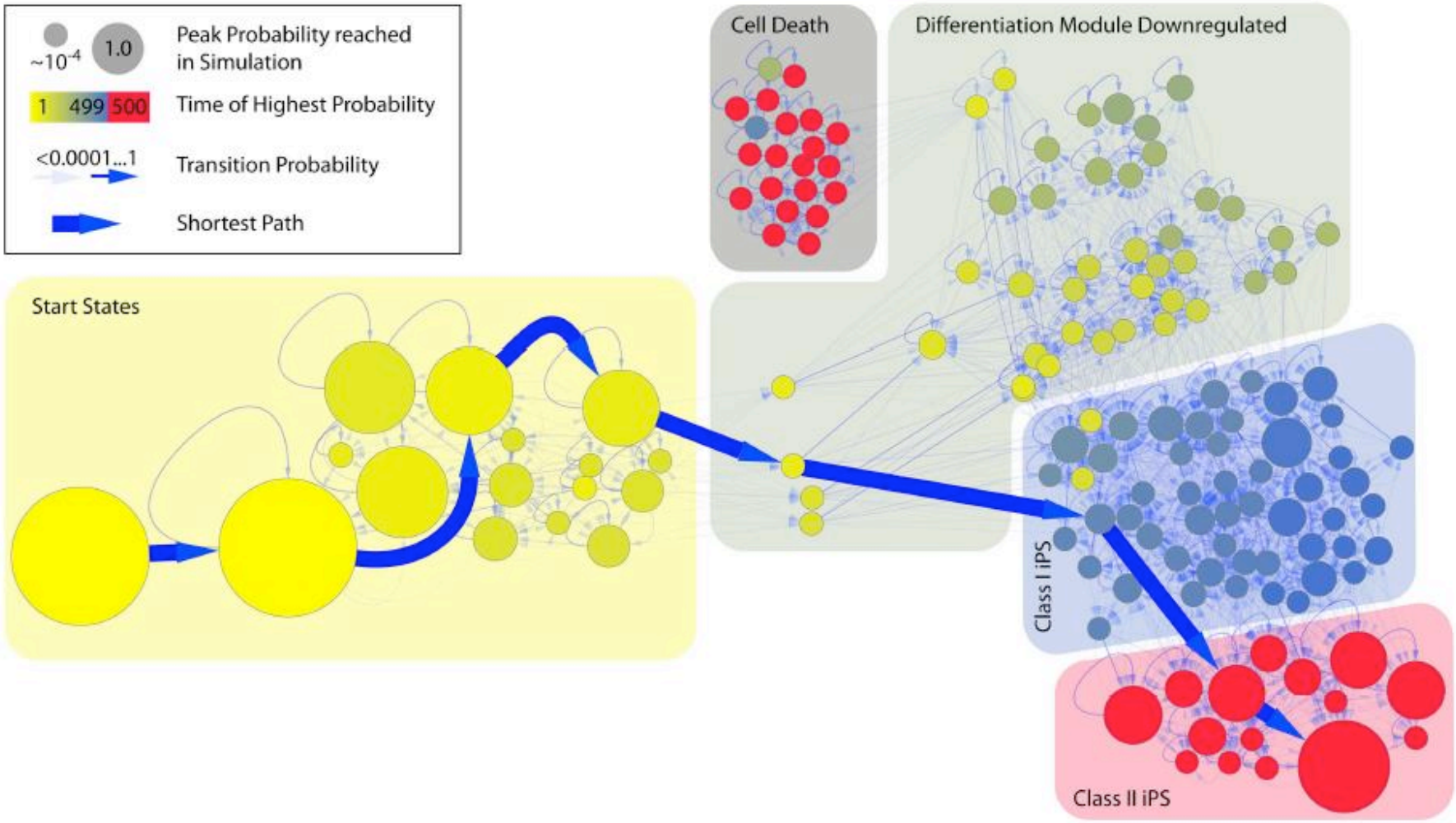
Developmental Pathway in State Space



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Reprogramming efficiency of the model variants

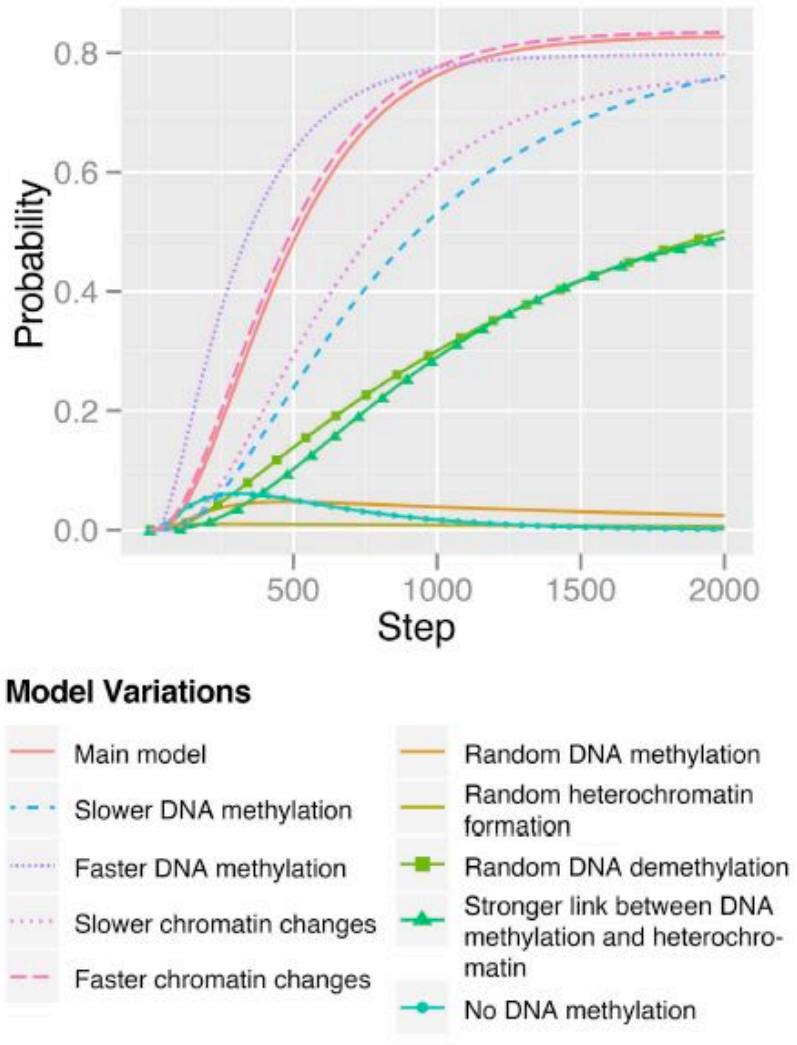

FIGURE 8 | Reprogramming efficiencies of the model variants. Efficiency is plotted as the sum of probabilities of all states that are closely connected to pluripotency.

In order to analyze the stability of the model and its behavior upon parameter variation, we varied the strength of the epigenetic modifications, i.e. , DNA methylation and chromatin changes.

We defined a parameter range including the parameters of our main model, a decreased and an increased probability of changes in methylation and heterochromatin formation and analyzed the effect on the reprogramming efficiency.

Interestingly, in the time range of 2000 time steps our main model nearly seems to have a maximal saturation for its reprogramming efficiency which is only very slightly surpassed by increasing the probability for euchromatin formation.

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Summary

Abstract models can mimick experimentally observed behavior of cell switching and of reprogramming to iPS cell state.

Sofar, no modelling presented at the level of individual genes.

Therefore, it is difficult to connect these early theoretical models with biological data.

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