A model for spread of epigenetic marks

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Herein we develop a stochastic model that describes the dynamics of epigenetic marks along a given DNA region and attempt to mathematically rationalise emergence of bistable and persistent epigenetic states from cooperative recruitment. We attempt to relate the rate of spreading of epigenetic marks from one site to another to power law contact probabilities between sites typically seen in polymers. The case of asymmetric interactions is also examined. Through stochastic simulation, we see how the bistability is affected by different power-law scalings. Some parallels are drawn between the dynamical system proposed herein and a 1D Ising model with long-range interactions.

I. INTRODUCTION

Cells are known to carry information handed down from their ancestors, and to pass it on to their descendants, primarily in two ways-either this information is encoded in the base pair sequence in the genome ("genetic"), or is mediated via a series of chemical modifications to nucleosomes, a basic unit of DNA packaging in eukaryotes, consisting of a segment of DNA wound in sequence around eight histone protein cores ("epigenetic")[1]. The former is the primary mechanism for information transfer over longer, evolutionary timescales, while the latter mediates memory over shorter time scales. Nucleosomes package eukaryotic DNA, with a density of about one nucleosome per 200 bp of DNA [2] [3], and the core nucleosome is composed of two molecules each of four core histones (H2A, H2B, H3, and H4) around which c.a.150 bp of DNA is wrapped [3].

Chemical modifications of nucleosomes come in many flavours (e.g., acetylation, methylation, or phosphorylation), and occur at different amino acid positions on the different histones. This confers a large information capacity on each nucleosome.

Additions and removals of these modifications are mediated out by classes of enzymes, like histone acetyltransferases (HATs), histone methyltransferases (HMTs), histone deacetylases (HDACs), histone demethylases [4] [5]

These modifications influence the activity of nearby genes in many ways. These modifications can affect the binding of regulatory proteins to nucleosomes, or they can influence the three-dimensional structure of the chromatin, encouraging it to exist in either a more compact (heterochromatin) or more open (euchromatin) conformation [3]. These effects can set up a positive feedback loop allowing nucleosomes that carry a particular modification to recruit either directly enzymes that catalyse similar modifications, or indirectly, by being simply more accessible to modifying enzymes by existing in a more open conformation.

The physical mechanisms that govern these biological processes behind the initiation, spreading, and inheritance of epigenetic states are extremely variegated and rich; they can involve changes in the molecular properties associated with the chemical modifications of DNA and histone proteins, such as methylation and acetylation, but also the physics that governs the three-dimensional organisation of the genome in cell nuclei. In order to achieve stability and heritability of epigenetic states, cells exploit several different physical principles, ranging from the universal behaviour of polymers, general features of dynamical systems, to the electrostatic and mechanical properties related to chemical modifications of DNA and histones. For an in-depth review of the subject one is encouraged to refer to [6]

II. THE MODEL

An attempt at modelling needs to capture three salient features: a) multistability (since epigenetic marks act as switches between different functional states). b) spatial patterns, and coupling between spatial conformation and reorganisation and spread of epigenetic marks. c) And finally, heritability [6]. In particular, we look at bistability, wherein different patterns of epigenetic marks allow one to switch between two states that have a well-defined functional characterisation. We consider a system of N nucleosomes that can be in n_s different states. The entire system is then consider as a polymeric chain of N nucleosomes, whose state is defined by the set of variables $\{s_1, s_2 \dots s_N\}$, with s_i denoting the state of i-th nuclesome in the chain, and we impose an overall constraint on the number of nuclesomes, $\sum_{j=1}^{n_s} n_j = N$, with n_i denoting the number of nucleosomes in state j. The model proposed herein, is a modification of work done by Dodd et al.[4] For instance, $n_s = 3$ corresponds to a nucleosome that can be either, "modified"(M, or $s_i = +1$), "unmodified"(U, or $s_i = 0$), or "anti-modified" (A, or $s_i = -1$). The analysis is indifferent to the actual identity of modifications involved. Nucleosomes can be actively inter-converted via four symmetrical positive feed-

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back loops (see FIG. 1. (a)), with one rate parameter α. The term recruitment is used in a general sense to imply that the presence of a modified nucleosome makes it more likely that another nucleosome in the region will carry the same modification. Nucleosomes can also be inter-converted in an independent recruitment manner ("noisy"). Again, we propose four symmetrical random noisy inter-conversions in the model (see FIG. 1.) with the parameter, $1-\alpha$. We define, $F = \frac{\alpha}{1-\alpha}$ as a ratio which is the critical parameter in the system.

We then introduce distance dependent cooperativity by making the rates of recruited inter-conversion reactions at each of nucleosome decay as a power-law dependence typical of the three-dimensional probability of contact, $r \propto P_{ij}(\gamma) \equiv \frac{1}{|r(i)-r(j)|^{\gamma}}$, where $r(k)$ defines the location k-th nucleosome. We then attempt to systematically look at the effect of γ on the bistability in our system.

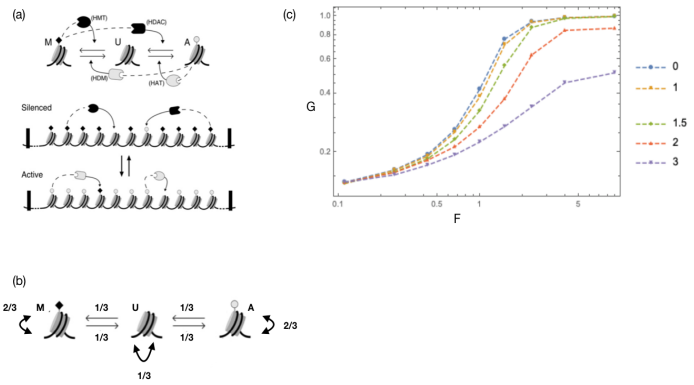

FIG. 1. (a) Schematic cartoon showing recruited conversion[4] (b) Schematic showing transition probabilities during noisy conversion (c) G plotted against model parameter F for $\gamma = 0, 1, 1.5, 2, 3$

A. Stochastic Simulation: Implementation

The stochastic simulation of the proposed model is carried out by iterating the following process of attempted modification of a nucleosome, as proposed by[4]

Step 1A: A random nucleosome n_1 is selected for modification from $N = 60$ total nucleosomes. With probability α, a recruited conversion of n_1 is attempted (Step 2A), OR with probability $1-\alpha$, a noisy conversion of n_1 is attempted (Step 2B).

Step 2A: Recruited conversion: A second random nucleosome n_2 is from within the $N = 60$, d positions away from n_1 with probability decays as $1/d^{\gamma}$, and if n_2 is in either the M or the A state, n_1 is changed one step towards n_2. The reaction schemes can be represented as follows:

n_1	n_2	Conversion ($n_1 \to n_1'$)
+1	+1	$\varnothing$
-1	-1	$\varnothing$
0	0	$\varnothing$
+1	-1	$1 \xrightarrow{\tilde{k}_1} 0$
0	-1	$0 \xrightarrow{\tilde{k}_2} -1$
-1	+1	$-1 \xrightarrow{\tilde{k}_3} 0$
0	+1	$0 \xrightarrow{\tilde{k}_4} +1$

Step 2B: Nucleosome n_1 is changed one step toward either of the other types, (barring direct $s_i = -1 \leftrightarrow s_i = +1$) interconversions with a probability 1/3. (see FIG. 1. (b)) Namely, when noisy conversion is being attempted the transition probabilities are given by $p_{M,U} = p_{U,M} = p_{A,U} = p_{U,A} = p_{U,U} = 1/3$ and $p_{M,M} = p_{A,A} = 2/3$.

1/3 probabilities in the previous step ensure that for $\alpha = 1-\alpha = 0.5$, the numbers of each type of nucleosome $A = U = M$, where we use A, U, M to denote the number of elements equal to $s = +1$, $s = 0$, $s = -1$.

A feedback-to-noise ratio, $F = \frac{\alpha}{1-\alpha}$ is defined, which contains information about the relative activities of the positive-feedback and noise-conversion processes. Although, one notes that for a given F, the actual ratios of recruited and noise conversions vary depending on the numbers of the three nucleosomes types at the time. Since F describes the tendency to order versus disorder, it can be thought of as a temperature.

We also need a metric to quantify the bistability by the broadness of the probability distributions of the number of M nucleosomes. We thus introduce a gap measure $G \equiv \left\langle \frac{|M-A|}{M+A} \right\rangle$ which is the absolute difference between the number of M nucleosomes and the number of A nucleosomes (normalised to the maximum possible difference). G values close to one signify a close-to-maximal spread of the distribution, indicating strong bistability, and in this sense, it behaves like a magnetisation (absolute value). Again we have used A, U, M to denote the number of elements equal to $s = +1$, $s = 0$, $s = -1$.

B. Results

As can be seen from FIG. 1. (c), the model is strongly bistable for $\gamma = 0, 1, 1.5$. Coincidentally, the curves for $\gamma = 0, 1$ coincide perfectly; $\gamma = 1.5$ coincides with the former only in limits of high noise (small F) or high recruitment (large F), with intermediate values showing some deviations. One notes the critical F_c is c.a. 1, with the F_c showing a tendency to increase with increasing γ. $\gamma = 2, 3$ is indicative of a system that is not bistable at all.

This behaviour is suggestive and leads one to draw parallels with an Ising model governed by the following Hamiltonian,

$$-\beta\mathcal{H} = \mathcal{K}\sum |i-j|^{-\gamma} s_i s_j \tag{1}$$

As first conjectured by Kac and Thomson [7], and shown by Thouless[8], Ruelle[9], and Dyson[10], such a Hamiltonian admits a phase transition at a finite temperature if and only if $1 < \gamma \leq 2$ (the case $\gamma = 2$ is special and requires some care). Perhaps there exists some correspondence, or mapping between the dynamical system prescribed herein and an Ising-like model with power-law long-range interactions and spin variables $s_i = \{\pm 1, 0\}$.

Our model with $\gamma = 0$ is essentially a high dimensional model since each site is coupled to every other site (during recruited conversion the second site is chosen uniformly at random from any of the other remaining sites). With increasing γ, the coupling between sites becomes more and more short-ranged, and eventually, it decays too fast to support bistability.

III. ATTEMPTS AT ANALYTICAL SOLUTION

We consider the system is divided into small cells denoted by the index i. Every cell can be occupied only by a restricted number of particles, which are subjected to special dynamical rules depending on the situation in mind. The starting point is the master equation, written as

$$\partial_t P(n,t) = L' P(n,t) \tag{2}$$

where P is the probability that a certain configuration characterized by the vector n at time t is realized. The evolution operator L' has to be specified by the dynamics of the model. Following the work of Doi[11] and others[12] the probability distribution $P(n,t)$ can be related to a state vector $||F(t)\rangle$ in a Fock space according to $P(n,t) = \langle n|F(t)|n|F(t)\rangle$ with the basis vectors $|n\rangle \equiv |n_1 n_2 \ldots n_I \ldots\rangle$. As a consequence, the master equation is is re-written as an equation in Fock space

$$\partial_t |F(t)\rangle = \hat{L} |F(t)\rangle \tag{3}$$

.

Some other useful relations [11],

$$|F(t)\rangle = \sum_{n_i} P(n,t) |n\rangle \tag{4}$$

where in order to derive these relations one notes the following $\langle s| = \sum_{n_i} \langle n|$, $\langle s|F|s|F\rangle = 1$ and $\langle s| \hat{L} = 0$ Typically, $\hat{L}$ is expressed using creating and annihilation operators which obey Bose commutation rules. However, to avoid double occupancy, we use the extension to the case of restricted occupation numbers per lattice site by introducing Pauli operators which commute at different points and anticommute at the same lattice point. Following methods prescribed in the literature [11–16] we attempt to cast our system in this formalism.

The dynamical system prescribed herein can be summarised by the following processes, at a lattice site indexed by i,

$$A_i(s_i = +1) \xrightarrow{\tilde{k}_1} U_i(s_i = 0)$$
$$M_i(s_i = -1) \xrightarrow{\tilde{k}_2} U_i(s_i = 0)$$
$$U_i(s_i = 0) \xrightarrow{\tilde{k}_3} A_i(s_i = +1)$$
$$U_i(s_i = 0) \xrightarrow{\tilde{k}_4} M_i(s_i = -1)$$

Here once again we note that spin-states corresponding to $s_i = +1$, $s_i = 0$, $s_i = -1$ are labbeled as states A_i, U_i, M_i for notational convenience. Now we introduce creation and annihilation operators $a_i^\dagger, u_i^\dagger m_i^\dagger$ and a_i, u_i, m_i. These commute at different points and anticommute at the same lattice point.

$$[b_i^\alpha, b^{\dagger\alpha}_i]_+ = 1 \tag{5}$$

$$[b_i^\alpha, b^{\dagger\beta}_j]_- = 1 \quad \alpha \neq \beta \text{ or } i \neq j \tag{6}$$

where b_i^1, b_i^2, b_i^3 corresponds to a_i, u_i, m_i respectively. Similar correspondence holds for the creation operators. The lower indices reference lattice points. One also defines number operators or indicators as,

$$\begin{aligned} \hat{A}_i &= a_i^\dagger a_i \\ \hat{M}_i &= m_i^\dagger m_i \\ \hat{U}_i &= u_i^\dagger u_i \end{aligned} \tag{7}$$

The rates of these process for the model proposed herein $\alpha\tilde{k}_q$ are the rates of recruited conversion given as,

$$\tilde{k}_1 = \sum_{i\neq j} P_{ij}(\gamma) \hat{M}_j$$
$$\tilde{k}_2 = \sum_{i\neq j} P_{ij}(\gamma) \hat{A}_j$$
$$\tilde{k}_3 = \sum_{i\neq j} P_{ij}(\gamma) \hat{A}_j$$
$$\tilde{k}_4 = \sum_{i\neq j} P_{ij}(\gamma) \hat{M}_j$$

$\hat{A}_j$ is an indicator (or number operators) such that they take the value 1 if spin at $s_j = +1$ (i.e. is in the state A_i) and zero otherwise. $\hat{M}_j, \hat{U}_j$ are defined similarly. What these rates imply is a particle at site i flips only if it interacts with a particle at site j according to the rules prescribed and appropriate weight. One then writes the time evolution equations as follows,

$$\partial_t \langle \hat{A}_i \rangle = \alpha \left(\sum_{i \neq j} P_{ij}(\gamma) \langle \hat{U}_i \hat{A}_j \rangle - \sum_{i \neq j} P_{ij}(\gamma) \langle \hat{A}_i \hat{M}_j \rangle \right) + \frac{1-\alpha}{3} \left(\langle \hat{U}_i \rangle - \langle \hat{A}_i \rangle \right) \tag{8}$$

$$\partial_t \langle \hat{M}_i \rangle = \alpha \left(\sum_{i \neq j} P_{ij}(\gamma) \langle \hat{U}_i \hat{M}_j \rangle - \sum_{i \neq j} P_{ij}(\gamma) \langle \hat{M}_i \hat{A}_j \rangle \right) + \frac{1-\alpha}{3} \left(\langle \hat{U}_i \rangle - \langle \hat{M}_i \rangle \right) \tag{9}$$

$$\partial_t \langle \hat{U}_i \rangle = -\langle U_i \rangle \left(\frac{2(1-\alpha)}{3} + \sum_{i \neq j} P_{ij}(\gamma) \langle \hat{A}_j \rangle + \sum_{i \neq j} P_{ij}(\gamma) \langle \hat{M}_j \rangle \right) + \langle \hat{A}_i \rangle \left(\alpha \sum_{i \neq j} P_{ij}(\gamma) \langle \hat{M}_j \rangle + \frac{1-\alpha}{3} \right) + \langle \hat{M}_i \rangle \left(\alpha \sum_{i \neq j} P_{ij}(\gamma) \langle \hat{A}_j \rangle + \frac{1-\alpha}{3} \right) \tag{10}$$

A. Mean Field Results

Under the mean field approximation terms like $\langle \hat{O}_k \hat{P}_l \rangle \approx \langle \hat{O}_k \rangle \langle \hat{P}_l \rangle$ [15].

1. *Case $\gamma = 0$, Mean field and uniform density approximation*

For a second if one forgets about the discrete lattice our system lives on, which seems reasonable for the case $\gamma = 0$ since we are interacting uniformly at random with any of our neighbours. In this case one can simply write down chemical rate equations using the principle of mass action (neglecting all spatial information). Here, x, y denotes the density of A, M nucleosomes respectively. Noting the density of U, A and M must add up to 1, we have only two independent chemical rate equations to worry about.

$$\partial_t x = (1-x-y) \left(x\alpha + \frac{1-\alpha}{3} \right) - x \left(y\alpha + \frac{1-\alpha}{3} \right)$$

$$\partial_t y = (1-x-y) \left(y\alpha + \frac{1-\alpha}{3} \right) - y \left(x\alpha + \frac{1-\alpha}{3} \right)$$

Which can be re-written in terms of our model parameter $F = \frac{\alpha}{1-\alpha}$

$$\partial_t x = -\frac{3Fx(x+2y-1)) + 2x + y - 1}{3(F+1)} \equiv p(x,y,F)$$

$$\partial_t y = -\frac{3Fy(2x+y-1)) + x + 2y - 1}{3(F+1)} \equiv q(x,y,F) \tag{11}$$

To obtain the stationary state solutions we set $p = q = 0$. This yields the fixed points. The system always admits a fixed point, at $x^* = y^* = 1/3$ regardless of the value of F. The fixed point at $x^* = y^* = 1/3$ changes from a stable fixed point to an unstable one as we change F. Above a certain F_c This is accompanied by the appearance of two new fixed points which are now stable. So we perform a linear stability analysis, by diagnolising the matrix of derivatives and computing its eigenvalues about the fixed point of interest.

$$M = \begin{pmatrix} \partial_x p & \partial_y p \\ \partial_x q & \partial_y q \end{pmatrix}_{x=x^*, y=y^*}$$

One of its eigenvalues is always negative, the second $\lambda = \frac{F-1}{3(F+1)}$ changes sign when $F_c = 1$, which very roughly agrees with $\gamma = 0$ case observed in the stochastic simulation.

2. *Parallels with Ising Model and phase transitions*

We have alluded to this previously. From a theoretical perspective, our model seems very similar to an Ising model where nucleosomal states represent spins (for example, M = 1, U = 0, A = +1), recruitment corresponds to coupling between spins (J), and "noisy" transitions correspond to thermal fluctuations ($k_B T$). We define an observable which behaves like magnetisation, $G = (x-y)$, and plot this versus F, which captures the ratio between the tendency to organise and tendency to thermalise. For the mean field uniform density case, we see a supercritical pitchfork bifurcation at $F_c = 1$ one would expect for

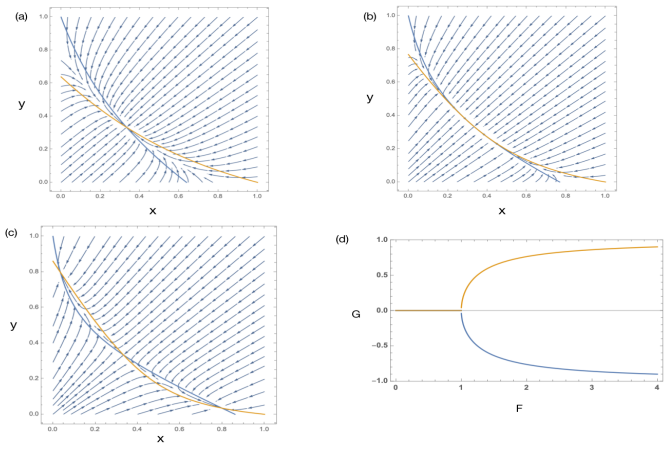

FIG. 2. Steady state solutions to (11) (Nullclines given by $p(x, y, F) = 0$ and $q(x, y, F,) = 0$)(a) $F = 0.3$ (b) $F = 1$ (c) $F = 2$ (d) G against F

a 1D Ising chain with long-range contacts. Our model with $\gamma = 0$ is essentially a high dimensional model since each site is coupled to every other site (during recruited conversion the second site is chosen uniformly at random from any of the other remaining sites). With increasing γ, the coupling between sites becomes more and more short-range, and eventually, it decays too fast to support bistability. All of this, however, is suggestive and is not a concrete mathematical mapping.

3. *Non-uniform case, $\gamma \neq 0$*

Introducing variables $x(i) = \langle \hat{A}_i \rangle$, $y(i) = \langle \hat{M}_i \rangle$ and noting $1 - x(i) - y(i) = \langle \hat{U}_i \rangle$. We only have 2 independent equations to worry about. The density $x(i)$ maybe thought of as the probability of i-th site to be in state A_i for example (since it is an expectation of an indicator function). Moreover, since $P_{ij}(\gamma) = |i-j|^{-\gamma}$ decays as we move further away from i, we can expand $x(j)$ and $y(j)$ about the point i using the discrete analog of a Taylor series (since our system lives on a discrete lattice).

$$\begin{aligned}\sum_{i\neg j} P_{ij}(\gamma)x(j) \approx x(i)\sum_{i\neq j}|i-j|^{-\gamma} + \Delta^1[x](i)\sum_{i\neq j}(i-j)|i-j|^{-\gamma} \\ +\Delta^2[x](i)\frac{1}{2}\sum_{i\neq j}(i-j)(i-j-1)|i-j|^{-\gamma} + \dots \\ \approx x(i)2\sum_{d\geq 1}^{L} d^{-\gamma} + \Delta^2[x](i)\sum_{d\geq 1}^{L} d^{2-\gamma} + \dots\end{aligned} \tag{12}$$

Here, $\Delta^n[f] = \sum_{k=0}^{n} \binom{n}{k}(-1)^{n-k} f(x+k)$ is the finite forward difference. A similar expansion can be carried out for $\sum_{i\neq j} P_{ij}(\gamma)y(j)$ term. The sums over d range up to some cutoff L where L is the maximum possible separation between two lattice sites. On a periodic lattice of N sites $L \sim N/2$.

For now, let us focus on the first order correction. The sum adds up to 1 since we are dealing with contact probabilities. Focussing on the first order term alone is tantamount to a uniform density approximation we have previously discussed for $\gamma = 0$. This is tantamount to washing away all spatial information.

The second order term, $+\Delta^2[x](i)\sum_{d\geq 1}^{L} d^{2-\gamma} + \equiv \eta$ evaluates to some number η_i, which we can treat as a perturbation to our particle density. This allows us to rewrite one pair of density terms appearing in the equation as, $x'(j) \to x(i) + \eta(i)$, $y'(j) \to y(i) + \eta(i)$. In general, this now depends on local variables $x(i)$ and $y(i)$ but for the sake of argument we assume this correction is sufficiently small that we are still close to the uniform density case. This should not be hard to realise near steady state.

$$\begin{aligned}\partial_t x(i) \approx (1 - x(i) - y(i))\left((x(i)+\eta)\alpha + \frac{1-\alpha}{3}\right) \\ -x(i)\left((y(i)+\eta)\alpha + \frac{1-\alpha}{3}\right)\end{aligned}$$

$$\begin{aligned}\partial_t y(i) \approx (1 - x(i) - y(i))\left((y(i)+\eta)\alpha + \frac{1-\alpha}{3}\right) \\ -y(i)\left((x(i)+\eta)\alpha + \frac{1-\alpha}{3}\right)\end{aligned}$$

Introducing our model paramter $F = \frac{\alpha}{1-\alpha}$, these differential equations can be recast into,

$$\begin{aligned}\partial_t x = -\frac{3F\eta x(2x+y-1)) + x(3F(x+2y-1)+2) + y - 1}{3(F+1)} \equiv f(x, y, F, \eta) \\ \partial_t y = -\frac{3Fx(\eta+2y) + 3F\eta(2y-1) + y(3F(y-1)+2) + y - 1}{3(F+1)} \equiv g(x, y, F, \eta)\end{aligned} \tag{13}$$

One then finds steady-state solutions, by setting $g(x, y, F, \eta) = f(x, y, F, \eta) = 0$. The system admits a fixed points, at $x^* = y^* = 1/3$ regardless of the value of F, η. The fixed point at $x^* = y^* = 1/3$ changes from a stable fixed point to an unstable one as we change F, η. This is accompanied by the appearance of two new fixed points which are now stable. So we perform linear stability analysis, by diagnolising the matrix of derivatives and computing its eigenvalues about the fixed point of interest.

$$M = \begin{pmatrix}\partial_x f & \partial_y f \\ \partial_x g & \partial_y g\end{pmatrix}_{x=x^*, y=y^*}$$

The relevant eigenvalues changes sign when $F_c = \frac{1}{1-3\eta}$. This corresponds to the fixed point at $x^* = y^* = 1/3$

changes from a stable to unstable fixed point, and two new fixed points appear. $\eta = 0$ recovers the mean field uniform density solution we derived for $\gamma = 0$. Also, since F cannot be negative based on its definition, our perturbation takes values between $0 < \eta < \frac{1}{3}$. For some finite acceptable value of η, F_c increases as expected. Since a power law decay is equivalent to reducing the coupling between sites, we need stronger feedback-to-noise ratios to achieve bistability. Qualitatively we have observed this in our stochastic simulation.

Unfortunately, these calculations failed to shed light on why $\gamma \geq 2$ fails to show bistability.

4. Asymmetric interactions

Suppose we push this argument it a little bit, namely that due to power law contact probabilities is similar to introducing an additive perturbation to our particle density. Also, assume for the sake of argument that marks A_i, M_i do not interact symmetrically. Namely, the rates are modified as follows.

$$\begin{aligned}
\tilde{k}_1 &= \sum_{i \neq j} P_{ij}(\gamma_1)\hat{M}_j \\
\tilde{k}_2 &= \sum_{i \neq j} P_{ij}(\gamma_2)\hat{A}_j \\
\tilde{k}_3 &= \sum_{i \neq j} P_{ij}(\gamma_2)\hat{A}_j \\
\tilde{k}_4 &= \sum_{i \neq j} P_{ij}(\gamma_1)\hat{M}_j
\end{aligned}$$

This would correspond to regions having predominantly A or M marks existing in more open or collapsed polymeric conformations, and thus have different power law contact probabilities between sites. This modifies our rate equations,

$$\begin{aligned}
\partial_t x &= \left(\frac{1-\alpha}{3} + \alpha(\eta_x + x)\right)(1 - x - y) - \left(\frac{1-\alpha}{3} + \alpha(\eta_y + y)\right)x \\
\partial_t y &= \left(\frac{1-\alpha}{3} + \alpha(\eta_y + y)\right)(1 - x - y) - \left(\frac{1-\alpha}{3} + \alpha(\eta_x x+)\right)y
\end{aligned} \tag{14}$$

One now has three parameters to tune F, η_x, η_y. The relative ratios of these parameters allows the system to switch between monostable and bistable regimes. At the steady state, the system has, at most, three fixed points, and the dynamical system is either monostable or bistable (with an unstable fixed point). For a given F which gives the balance between recruited and noisy conversions, depending on the asymmetry between η_x and η_u the chromatin persists in a particular epigenetic state

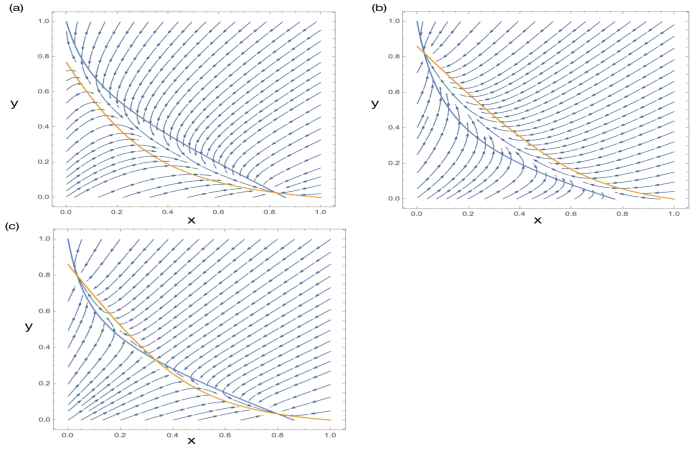

FIG. 3. Steady state solutions with asymmetric interactions given $F = 2$ (a) $\eta_x = 0.3, \eta_y = 0.16$ (b) $\eta_x = 0.16, \eta_y = 0.16$ (c) $\eta_x = 0.16, \eta_y = 0.3$

over the other. A similar model with asymmetric reaction rates, which exhibits similar behaviour has been considered previously[17]

IV. DISCUSSION

In this work, we proposed and analysed a simple, microscopic model for the spread of epigenetic marks. We related the dynamics to power law contact probabilities that are typical for a polymer chain, and through mathematical analysis were able to show that system could exist in either monostable or bistable states by tuning the model parameters. Through stochastic simulation, we also observed that the system is only bistable when the scaling exponent is $\gamma < 2$. Unfortunately, we were unable to rationalise this in our analytical solutions. Some parallels with a 1D Ising Model were observed, and it would be interesting to make a concrete mathematical mapping between the two, provided such a mapping is indeed possible.

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