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Cancer: A Turbulence Problem

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CANCER: A TURBULENCE PROBLEM

ABSTRACT

As we transition towards an era of Computational Medicine and Deep Learning Healthcare, our mathematical models of cancer dynamics must be revised. As such, recent evidences support the perspective that cancer-microenvironment interactions consist of turbulent flows and strange attractor dynamics. Using a systems biology approach, cancer pattern formation, energy flow, protein folding kinetics, stem cell fate bifurcations and metastatic invasion are hereby discussed within the context of hydrodynamical turbulence. Cancer is presented as a three-dimensional Navier-Stokes equations global regularity, smoothness and existence problem.

INTRODUCTION

Cancer is a complex dynamical system. The heterogeneous clonal expansion, replicative immortality, patterns of longevity, evasion of death signals, hijacked immune system, self-sufficient growth signals, metastatic invasion and other emerging hallmarks of cancer indicate it is a highly adaptive system (1). Our current statistical methods in modelling cancer energy landscapes mainly comprise of Bayesian inference, stochastic gene regulatory networks (graph theory), information entropy, Monte Carlo methods, machine learning algorithms, signal processing and cluster analysis (2, 3). An example is the Kauffman NK model, a tunable rugged landscape in combinatorial phase space used to describe the gene networks as an optimization problem (4). Hence, we adopted a stochastic view of gene expression dynamics, especially given the Brownian motion underlying the chemical kinetics and signal transduction is a stochastic differential equation. Computational tools and machine learning algorithms for analyzing signaling flow is rapidly evolving. For example, with the use of single-cell RNA sequencing and PCA (protein complementation assays), gene expression flows of GRNs (Gene Regulatory Networks) between heterogeneous stem cell populations and their microenvironment can be graphed (5). However, the possibility of nonlocal cross-talks between these networks remains a query.

For instance, GSC (glioma stem cells)- EC (endothelial cells) interactions regulate cancer stemness, tumor propagation and therapy resistance via dynamic reciprocity (i.e. feedback loops with the ECM-cytoskeleton). Such complex dynamical systems have been modelled using simple reaction-diffusion-advection equations such as Darcy's law (a simplified Stokes equation) (6). Using a mass conservation equation and focal adhesion energy, recent 3D modelling of glioblastoma shows vascular-endothelial interactions result in tumor relapse and chemoresistance (6). However, it is assumed such interactions occur with low Reynolds number and laminar flows. Laminar flow is only a subset of the intermittency observed in turbulent flows.

Moreover, many of the fundamental issues in the study of cancer dynamics remain unsolved foundational problems in physics. The stochastic interconversion of intermediate (mixed) phenotypes during EMT/MET (epithelial-mesenchymal transitions), their niche-dependent reversibility and quantification in time is an unsolved problem. The same problem of stochastic heterogeneity applies to tracking cancer stem cells, dormant circulatory tumor cells, secretory vesicles/exosome flow and

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partially reprogrammed, metastable attractors in the epigenetic landscape of induced pluripotent stem cells- iPSCs (7,8).

The perspective proposes that we must adopt a paradigm shift towards viewing cancer cell communication networks within the scope of fluid dynamics, whereby their information flow may be best described as 'turbulence'. Namely, cancer morphogenesis, energy flow (i.e. angiogenesis and nutrient supply), metastatic invasion (focal adhesion dynamics), cancer stem cell remodelling and protein folding are few examples of cancer-related processes exhibiting turbulence.

The role of chaos in complex adaptive systems such as cancer is emerging (9). Cancer cells adapt rapidly to extreme conditions, partially owing to their heterogeneous, asymmetric stem cell division and proliferation. Cancer stem cells are complex attractors on the Waddington epigenetic landscape (10). Hopfield (1982) first pioneered the principle of emergent collective behaviours in cybernetics using spin glass statistics (11). The Hopfield neural network is essentially an energy landscape resembling the configuration space of the Waddington developmental landscape, whereby the Lyapunov energy minimization predicts the local attractors (12, 13). Classically, due to the stochastic nature of molecules, the transitions between the attractors are defined by random walks on a network (14). The fluctuations around the epigenetic barriers of the energy landscapes are governed by diffusion equations. More specifically, the Fokker-Planck equations, Freidlin-Wentzel theorem and FDT (fluctuation-dissipation theorem) (8, 15). Once again, our models adopt a stochastic approach to cell state bifurcations on the Waddington landscape due to the underlying principle of Brownian motion. The cell fate trajectories of cancer stem cells at the critical state transition point are characterized by a bifurcation parameter μ, whereby the dynamics of the system in attractor space (in one dimension) is given as $\dot{x}(t) = F(x(t), \mu)$ (16, 17). The observables of a system approaching a bifurcation can often be quantified as an increase in the amplitude and temporal autocorrelation of the stochastic fluctuations.

The distribution of possible paths followed by a random walk on a GRN network can be in three forms: finite, stretched exponential and power law (14). The latter two are used to describe the strange attractor dynamics of weather turbulence (i.e. Lorenz attractor) and protein folding (14). It must be noted that the Lorenz attractor is a toy model of deterministic chaos (i.e. sensitive dependence on initial conditions) (18). As such, chaotic dynamical systems exhibit seemingly 'apparent randomness'. The Navier-Stokes Equations (NSE) smoothness and existence problem lies within this description (19). By convention, the protein folding free energy landscape is defined as a stochastic process with Ising spin glass formulation (20). However, the power law decay observed in protein folding kinetics is a signature of turbulence in experimental fluid dynamics (14, 21). Cancer is hereby presented as a complex dynamical system exhibiting turbulence at every scale, i.e. strange attractors (Figure 1).

HYPOTHESIS: *Cancer cells are strange attractors in the Waddington landscape exhibiting turbulence.*

TURBULENCE

By definition, turbulence is the flow patterns of a fluid motion with chaotic changes in pressure and velocity. Turbulent flows are dissipative systems exhibiting strange attractor dynamics (21). The Reynolds number measures the ratio of kinetic energy to viscous damping of flow. In the NSE, the

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nonlinear inertial term $(u \cdot \nabla)u$ competes with the viscosity term $v\Delta u$. The competition is characterized by the Reynolds parameter as $Re = \frac{Lu}{v}$. The Reynolds number varies from systemic circulation to cellular dynamics since biosystems comprise of multiple flow patterns at different scales (22, 23). The Navier-Stokes equations for 3D isotropic, homogeneous turbulence are given by $\frac{\partial u}{\partial t} + (u \cdot \nabla)u = v\nabla^2 u - \frac{\nabla P}{\rho} + f$ and the incompressibility condition $div\, u = \nabla \cdot u = 0$, where v= kinematic viscosity, f= external force, P= pressure, ρ= density, ∇= gradient and u= velocity field.

How high must the Reynolds number be for the system to be turbulent? This remains an unsolved problem indicating the turbulence problem is fundamentally a scaling problem. Even at smaller scales pertaining to biological processes, we observe the Richardson-Kolmogorov energy cascade (24). The Karman–Howarth (vortex street) equation was shown to best-describe the power law decay in numerical simulations of low Reynolds, isotropic homogeneous turbulence (22).

The dynamical self-organization of many microbiological systems exhibit self-sustained incompressible, active turbulence in nutrient mixing and molecular transport (25, 26). The Vicsek model is often used to describe the collective motion and flocking of such active matter. However, recent findings suggest the Navier-Stokes equations with a cubic nonlinearity may better model the self-organized pattern formations of active matter in biosystems. Active turbulence could potentially explain the collective cell migration and focal adhesion dynamics of cancer cells with the ECM. Cancer migration is governed by cell polarity complexes and Cdc42/Rho-GTPases/Rac system regulating actomyosin contractility (27, 28). The actin cytoskeleton is being recognized as active matter (29). Turbulent-like flows at low Reynolds numbers also applies to microtubule-filaments motor dynamics. Their energy cascades produce vortex tangles with lesser intermittency (23). Reconstituted cytoskeletal solutions of microtubules and kinesin nematics show active turbulence with a quadratic variant of the Kolmogorov hydrodynamical equations (30).

Reaction-diffusion equations model pattern formation in biosystems. Turing (1952) first defined morphogenesis using a set of nonlinear partial-differential equations characterizing the activator-inhibitor dynamics of morphogen gradients (31). Tumorigenesis is a subset of morphogenesis exploiting this property to attain non-equilibrium patterning. The general Reaction-Diffusion equation for tissue patterning is given by:

$$u_t = F(u, x, y, z, t) + D\Delta u$$

where D is the diagonal matrix of Diffusion coefficients, F is the local reactions of chemical species and u is the velocity field. The Turing pattern formation for two-chemical species (u and v) is given by:

$$\frac{\partial u}{\partial t} = F(u.v) - du + D_u \Delta u$$

$$\frac{\partial v}{\partial t} = G(u.v) - dv + D_v \Delta v$$

The equations state that the Rate of change of u and v = Production- (degradation+ diffusion) terms (i.e. F and G describe the production and D= diffusion coefficients).

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The Lotka-Volterra- predator prey dynamics are simple 1st order differential equations describing populations change through time according to their growth rates given by:

$$\frac{dx}{dt} = ax - \beta xy$$

$$\frac{dy}{dt} = \delta xy - \gamma y$$

(x and y are coordinates of two species, t= time and the remainder are growth/decay parameters). Smale (1976) showed that with N≥ 5 chemical species at certain conditions, the Lotka-Volterra model gives rise to asymptotic behaviours seen in experimental fluid dynamics. As such, complex Hopf-Turing bifurcations occur forming *strange attractors*. Cancer being a complex, heterogeneous niche of dynamical phenotypes, the applicability of strange attractors must be self-evident. A simple reaction-diffusion model that incorporates the predator-prey dynamics and Feigenbaum (logistic map) bifurcations is the Fisher-Kolmogorov-Petrovsky-Piskunov (FKPP) equation. It was initially used to describe the spatial spread of an advantageous allele in terms of its nonlinear travelling wave solutions (32, 33). The FKPP equation for N-chemical species is given by:

$$\frac{\partial N(x,t)}{\partial t} + \nabla \cdot (VN) = \gamma N\left(1 - \frac{N}{K}\right) + \nabla \cdot (v \nabla N)$$

γ is growth rate of population, K carrying capacity, v spatial parameter, u the velocity field and ∇ is the gradient. The NSE (Navier-Stokes Equations) exhibit very complex, multi-nested bifurcations as well, where the competition is between the nonlinear velocity and viscosity terms (21).

Ruelle (1995) described non-periodic cases of chemical oscillations exhibiting chaotic dynamics (21). Such turbulent chemical oscillations may be the problem underlying cancer pattern formation. Experimental turbulence exhibits three properties: (a) A continuous frequency spectrum, (b) Intermittency- the transition between laminar and chaotic flow regimes, and (c) Nonlinear resonances and nested, multi-fractal structures describe its complex bifurcations (i.e. statistical self-similarity) (21, 34). All three properties can be summarized as 'strange attractor' dynamics (21).

If we adopt the Ruelle-Takens route to chaotic, dissipative dynamical systems, we can map turbulent flows as the destruction of resonant tori (21). The quasi-periodic motion of the system X is given by $\frac{dX}{dt} = X_\mu(t) = f(\omega_1, \ldots., \omega_k, t)$ where μ is the Reynolds number (bifurcation parameter) and ω the oscillation frequency. Note this equation is identical to the above-discussed dynamical systems characterizing cell fate bifurcations in the Waddington landscape (7, 16). The correlation function of the system in frequency-space is expressed as

$$\widehat{\rho_s}(t) = \int dt\, e^{i\omega t} \rho_s(t)$$

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where ρ is the signal density distribution and τ is the blow-up time/ critical (phase) transition point. Then, given u =velocity field, a continuous power spectra is observed in frequency-space with Dirichlet Boundary conditions:

$$S(\omega) = C \lim_{\tau \to \infty} \frac{1}{\tau} \left[\int_0^\tau dt e^{i\omega t} u(t) \right]^2$$

Interestingly, for flows obeying Axiom A diffeomorphisms, with Gibbs mixing, complex poles emerge as resonances. The resonances are related to the Riemann Zeta function (21).

SYMMETRY-BREAKING

Pattern formation in biological fluids exhibit spatio-temporal chaos and is an emerging class of turbulent flows (21, 35). There are many orders of magnitude difference in the diffusion coefficients between the membrane-bound and cytosolic conformations of these proteins due to the complexity of the fluid model and the multi-scale interactome. Although cellular automata can model the NSE without any partial differential equations, they are models inspired by and limited to a sub-class of pattern formations observed in nature (36).

The French-Flag model and Clock & Wavefront model are often used to visualize the patterning of embryonic developmental cascades such as Wnt, Notch and Hedgehog (37, 38). These pathways are core factors in the EMT program controlling stem cell bifurcations and cancer stem cell niche homeostasis (39-41). The cross-talks between the niche pathways determine phenotype plasticity and are attractors for the epigenetic reprogramming of cell fates (42, 43). These mathematical models assume the chemical oscillations of such morphogens behave as periodic, harmonic oscillators. However, they are non-harmonic (nonperiodic) oscillators postulated to exhibit strange attractor dynamics in cancer. In support of this argument, using finite elements method, Halatek and Frey (2018) showed that the reaction diffusion systems of an E. coli pattern formation complex- the Min system- must undergo an initial phase of turbulent flows characterized by the Kolmogorov-Richardson energy cascade (44).

Simulations of the Min system showed that at the critical transition time (bifurcation), the propagating wavefront triggers an energy cascade of destabilized local equilibria entering a turbulent state whereby all state dynamics of the kymogram are spatially uncorrelated (44). The Min protein complexes are key regulators of cell polarity and asymmetric stem cell division. The mammalian orthologue of these proteins are known as PAR complexes. The PAR 3/6- aPKC complexes are determinants of stem-cell fate choice. They interplay the self-renewal and cleavage of cancer stem cells through feedback loops between the mitotic spindle network, cell cycle and cytoskeletal-ECM (Extracellular Matrix) remodelling pathways (45). Hence, it may be self-evident to postulate that a greater level of turbulent flows must occur in the chemical oscillations of such symmetry-breaking protein complexes in the chaotic patterning of cancer tissues.

Moreover, metastatic invasion and focal adhesion dynamics is tightly regulated by the energy cascades of turbulence equations (46). Non-laminar shear stress and turbulence may increase the adhesive

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ability of cancer cells in metastatic invasion through cross-talk between actin-cytoskeletal reorganization and polarity complexes (46, 47) (Figure 2). For example, higher streams of vascular flow induce aggressive phenotypes in ovarian cancer models by promoting EMT (48).

FRACTALS AND CHAOS

The increased stochastic heterogeneity in the methylation profiles of cancer drives its cell fate trajectories (49, 50). The term turbulence has been used to describe the aberrant histone/chromatin remodelling during ageing and such heterogeneity equally applies to the transgenerational epigenetic inheritance of cancer (51). It has been well-established that the time-frame required for a benign tumor to evolve into malignant phenotypes varies from patient to environment, ranging from months to years. If cancer evolution is a time-driven transformation, sensitively dependent on its initial mutations (i.e. Driver mutations), it is a chaotic process. There are at least 1-2 orders of magnitude difference in the frequency of epimutations vs. somatic mutations in cancer (52). There is some degree of chaos in the cancer stem cells clonal selection explaining this heterogeneity, which amounts to the time-variability in division rates and gene expression of each cell (9). Another problem is tracking the reversible, mixed-transitory phenotypes which opens to question the plausibility of non-local cross-talks between the cancer stem cells and their niche.

Cancer nutrient supply is mediated through angiogenesis, lymphatics and vasculogenic mimicry, which exhibit fractal structures. Angiogenesis is a crucial survival mechanism under hypoxic conditions interlinking the Warburg effect and metastasis (53, 54). Fractal image analysis techniques show tumor vasculature is primarily determined by heterogeneity of the ECM (niche) rather than by gradients of diffusible angiogenic growth factors (55). Thus, in hypoxic conditions, tumor vasculature responds by growing into an extended fractal network through a heterogeneous ECM (i.e. invasion percolation) (55, 56). The notion of higher fractal dimensions is intertwined to increased turbulent flows, as should be the case for cancer dynamics for intrinsic (pattern formation/chemical oscillations) and extrinsic (vasculature) parameters (34). It is well-established increased turbulent fluid circulation is a signature of pathological conditions at systemic scales (57, 58).

The concept of stimulating a core set of transcription (Yamanaka) factors to induce pluripotency revolutionized regenerative medicine and systems biology (59). One of the current obstacles in iPSC generation is overcoming the epigenetic barriers causing its low interconversion rates, heterogeneity and genomic instabilities/mutations (60, 61). We now know many alternate algorithms (biochemical networks) exist to reprogram cells to pluripotency (62). Recent findings suggest that mechano-transduction from the niche/ECM (extracellular matrix) reprogram cells to iPSC states (63).

Ito et al. (2018) experimentally demonstrated turbulent flows in the cell environment can increase the level of iPSC production in hematopoietic stem cells (64). Turbulent flow generating turbines and microPIV (particle imaging velocimetry) techniques were used to increase the production of platelet-forming stem cells (64). As such, we can further speculate that cancer stem cells may be exploiting turbulent flows in their surroundings through the various mechanisms discussed hereby such as angiogenesis/nutrient supply, pattern formation and metastasis to confer their microenvironment-specific adaptive advantages.

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POWER LAWS

In classical homogeneous turbulence, the Kolmogorov energy spectrum is given by a power law decay $E(k) = C\varepsilon^{2/3}k^{-5/3}$ in the inertial range, where C is some constant, ε the energy flux and k is the wavenumber (65). In other words, energy is dissipated at a rate of ε at the Kolmogorov wavenumber. This forms the Richardson cascade, where large-scale flow structures (eddies and vortices) decay into smaller structures. As mentioned, we are currently adherent to the dogma of visualizing protein folding as a stochastic process. However, the simulated protein folding transitions of SH3-domain (Src Homology 3) protein was shown to obey the vortex dynamics and hydrodynamical equations of Kolmogorov's statistical theory of turbulence (66-68). The spatial flow distributions of the probability fluxes were determined to be self-similar (Kolmogorov-Richardson cascades) with a fractal dimension that decreases toward the native state, indicating that paradoxically the flow becomes more turbulent at more stable protein conformations (67, 68). Interestingly, most focal adhesion complexes and tyrosine receptor kinases mediating the initiation and progression of cancer metastasis depend on the structural conformation of SH3 domains (e.g. Src/FAK/Crk/Cas pathways) (69). These pathways cross-talk with crucial attractors regulating the growth, metastasis, protein synthesis and homeostasis of cancer cells such as the mTOR (mammalian Target of Rapamycin) pathway (70).

The loop extrusion model shows that SMCs (Structural Maintenance Complexes) such as cohesin/condensin self-organizes chromatin remodelling during mitotic division as a power law decay described in terms of the spacing s as $P(s) = e^{-0.5s}$. These findings indicate that the mitotic chromosome is in between an equilibrium globule of highly mixed (heterogeneity) and fractal (spatially segregated, self similarity) module (71). Such models of complexity are known as hyper-uniformity.

Furthermore, power law decay is a signature for the emergence of self-organization in many edge of criticality phenomena such as the Metal-Insulator transitions and semi-classical processes. The transition from quantum to classical chaos in such systems forms a power-law decay (72). Power law decays may explain the extended quantum coherence and quantum transport observed in phenomena associated to the newly emerging field of quantum biology such as the photosynthetic energy transfer of chromophores at room temperature (73, 74).

COMPLEXITY AND EMERGENCE

The field of oncology is rapidly evolving due to interdisciplinary techniques. Over the past decade, we've seen advances in oncology pertaining to nanoparticle drug-delivery, CRISPR-Cas9 genome editing and oncolytic viral therapy/immunotherapy to name a few (75, 76).

The role of microRNAs in reprogramming cancer phenotypes is well established. Tumor-suppressive miRNAs with guide strands containing a G-rich toxic 6mer seed were recently discovered and may potentially eliminate cancer cells (77). The master tumor suppressor miR-34 is a G-rich 6mer seed. For instance, SNAIL-1/TGF-β and miR-34 form a bistable switch for EMT. This feedback loop may explain the EMT reprogramming of intermediate, mixed phenotypes in cancers (78).

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The spreading of (dormant) circulating tumor cells (CTCs) through vascular and lymphatic circulation partially explains the recurrence of cancer metastases, accounting for 90% of cancer-related death. Micro/Nanofluidics have revolutionized our way of understanding CTC dynamics and metastatic invasion. Recent findings suggest that methylome analysis of the circulating tumor DNA (ctDNA) are diagnostic indicators of cancer (79). In principle, constructing a Hopfield-Deep learning network that can assess the differences in the methylome patterns of plasma ctDNA in cancer patients may pave early detection. We are approaching an era of computational oncology where artificial intelligence and Deep Learning networks are the emerging frontiers of precision medicine and personalized pharmacogenomics (80) A recent example is IBM Watson Health's cancer AI algorithm (81).

Another emerging hallmark of cancer is the flow of heterogeneous, nano-scaled exosomes throughout its evolution. Single-exosome isolation and characterization may be revolutionary to early detection of many diseases including cancer. Exosomes may not only help unravel the complexity of cancer-environment communication but also explain why cancer cells evade the immune system. Thereby, exosomes are a target for effective immunotherapies (82). Moreover, human embryonic stem cells-derived exosomes can reprogram malignant cancer phenotypes to benign-like fates (83). Perhaps we shouldn't reduce complex dynamical systems such as the cancer-microenvironment to specific 'hallmarks' since these are merely emergent, adaptive properties exhibited by the phenotypic plasticity of cancers. For instance, certain malignant melanomas spontaneously regress, a property not recognized as a hallmark (84). For instance, PEDF (pigment epithelium derived factor) expressed by extracellular vesicle bodies-mediated EGFRvIII (i.e. horizontal malignant trait transfer) promotes the self renewal and propagation of GSC (85, 86). However, PEDF is an anti-angiogenic factor and GSC require vascular interactions for development. Such complex feedback loop rewiring is not defined in the early set of hallmarks. Some cancers adapted to fatty acid metabolism as opposed to Warburg effect. Recent findings show non-target specific chemotherapy causes cancer cells to release pro-metastatic exosomes. Hence, exosomes transfer chemoresistance and monitor cancer microevolution (87).

How do we assess the driver-mutations network of a cancer with limited sequencing data? This is an optimization problem of the cancer attractor landscape. These are fundamental road-blocks in machine learning algorithms and graph theory pertaining to the P vs. NP problem. Many such NP-hard problems exist in computational complexity within cancer networks and cybernetics (88).

Cytokinesis defects form aneuploidy and genomic instability in cancers. The tetraploid cells generated through cytokinesis defects serve as intermediate states on the route to genetic diversification/heterogeneity (89). Furthermore, a Tubulin Code hypothesis is proposed to explain the computational complexity of cancer cell division (90). Surprisingly, cancer cells show upregulated MAPs (microtubule associated proteins) and an absence of PTMs (post-translational modifications) on HeLa cancer cells (90). The implications of these findings in the phenotypic plasticity and immortalized (in vitro) regenerative potential of HeLa (in addition to telomerase overexpression) remain unanswered.

On a final note, Quantum biology is an emerging field subjected to controversy (91). Fundamentally everything is governed by quantum mechanics, including mutagenesis (92). However, this emerging field asserts that macroscopic quantum effects may occur in biosystems at ambient temperatures, indicating there is a scaling law problem as seen with turbulence (93). Of the many models in support of this field, the most controversial and most pertinent to cancer dynamics is the plausibility of quantum coherence

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in microtubules (94). Although it severely lacks any empirical evidence, it is worth noting that if nonlocality of microtubules is plausible at physiologically relevant temperatures, their signaling cascades may be crucial attractors in the phenotypic reprogramming of cancer-ECM.

CONCLUSION

In conclusion, given the evidences in support of the thesis, Cancer cells are proposed to be strange attractors in the Waddington landscape whereby turbulence unifies their dynamics at all scales (processes). The reaction-diffusion equations of critical signaling events in cancer morphogenesis and related processes (e.g. EMT, asymmetric stem cell division, differentiation and metastatic invasion) exhibit turbulence. Then, the hydrodynamical solutions to the three-dimensional Navier-Stokes equations is crucial for understanding the complex cancer cell-fate bifurcations in the Waddington landscape. Therefore, in principle, using genome editing techniques (e.g. CRISPR-Cas9), single-cell RNA Seq (transcriptome profiling), epigenomic profiling and microfluidics, we can predict the GRNs that may allow the phenotypic reprogramming of cancer. If the presented perspective is further validated, such attractors must be potential barriers (valleys) where the most turbulent flows are observed in the epigenetic landscape. In other words, the chemical oscillations of such signaling cascades must exhibit strange attractor dynamics.

Hence, the turbulence equations will help us navigate the attractor space of GRNs regulating cancer stem cell niches. The heterogeneity problem can then be overridden by identifying these attractors in the GRN for cancer stem cell niches resulting in phenotype reprogramming (Figure 3). For instance, the epigenetic landscape of GBMs (Glioblastoma Multiforme) shows tremendous spatiotemporal heterogeneity (95). However, a core set of neurodevelopmental transcription factors (POU3F2, SOX2, SALL2, OLIG2) were identified to be essential for GBM propagation in brain cancer stem cells (96).

In the mean time, current treatments for oncology patients must be such that post-systemic screenings and tumor biopsy, the following must be performed: tissue immunohistopathology, cytogenetics and genetic (DNA mutations) profiling to assess the optimal target-specific therapies for the patient's cancer (i.e. personalized pharmacogenomics). Once potential driver mutations are identified, at least a cytotoxicity assay on a 3D cell culture/spheroid of patient's tumor biopsy with screened target-specific drugs can be performed in comparison to regime chemotherapies for efficacy, prior to therapeutic administration (97). Genome-editing tools such as CRISPR can serve as a drug screening platform. Our recent advances in ctDNA and exosomes tracking will pave minimally invasive liquid biopsies.

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DECLARATIONS: I, Abicumaran Uthamacumaran, am the sole author of the submitted perspective/paper. There are no competing interests.

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FIGURES LEGENDS

Figure 1: Waddington landscape- The Waddington landscape shows a stem cell S bifurcating to various cell fates represented by the blue balls. As seen in red, the flows of gene expression underlying the differentiated cell states S1 and S2 seem more laminar. However, cell fates are reversible as indicated by the dotted line. Multiple bifurcation routes exist towards a local energy minimum X which shows highly turbulent flows in its underlying gene regulatory network expressions. The attractor X is a chaotic cell fate (i.e. cancer). Hence, cancer is shown as a strange attractor on the developmental landscape.

Figure 2- Focal Adhesion Dynamics: The discussed Src/FAK (focal adhesion kinase) ECM (extracellular-matrix)- remodelling pathways and its cross-talk with cytoskeletal remodelling cascades are shown. The cell-polarity complex PAR is a key player, which recent evidences show undergoes turbulent flows during the symmetry breaking of tissue pattern formation. These pathways regulate cancer morphogenesis, asymmetric stem cell differentiation/self-renewal, EMT (epithelial-mesenchymal transitions) and metastatic invasion.

Figure 3- Cancer Stem Cell Niche: A simplified representation of the cancer stem cells' local microenvironment. Morphogens pertaining to the EMT program such as the Wnt/βcatenin pathway, Notch, VEGF, HIF-1, ECM (extracellular matrix)-remodelling pathways, etc. are shown to induce phenotypic plasticity and regulate the iPSC (induced pluripotency stem cell) network of Yamanaka factors (Oct4, Sox2, c-Myc, Klf4). Moreover, they form feedback loops with the ECM-stroma focal adhesion pathways, differentiation & cancer-growth pathways (mTOR).

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