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Cancer Clonality and Field Theory

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A field theory [1] models malignancy as a state "added" to, and capable of interacting with, other normal states composing the field associated with any living cell. The theory may be downscaled from the (multi) cellular to the level of topologically disordered motions of chromatin and DNA strings occurring before or at interphase when chromatids are iteratively dilated in cells mitotically driven by a potential from special "source" cells. Clonal development of tumors might result from the extremely low efficiency with which the driving potential activates its corresponding gene(s) P in one (or exceedingly few) source-dependent cell. Most normal cells are assumed to have gene P "curled up" in some nonexpressed configuration in a segment j (say) within a lattice or plaquette unfolded from crumpled preimages during chromatid decondensation [11–13]. Through anharmonic, intermittent (generally frequency-incommensurable) stimulations from exogenous potential and after N mitoses, segment j might percolate in a rare cell into a less entangled chromatin phase, arbitrarily called "active or ballistic layer," where the probability for expressing P increases.

Chromatin loops are envisioned to reptate within a *finite* subvolume of the cell nucleus with snake-like, intermittent multicollisional motions [2], analogous to "string animals" described, for example, by Suzuki [3]. The kinematics of string subsections, including those of segment j imprinted by gene P, are modeled thus by a "master" equation [3]:

$$\frac{\partial}{\partial t} P([x_j], t) = -\Sigma_j W_j([x_j]) P([x_j], t) + \Sigma_j W_j([x'_j]) P([x'_j], t),$$

Therein, $P([X_j],t)$ may be roughly understood as the time-dependent probability for segment j to acquire a conformation optimal for expressing P out of $[X_j]$ configuring motions, and $W_j([X_j])$ as the transitional probability for segment j to percolate across the interphase "mass of string segments" during iterated chromatid unfoldings. Hence, the equation couples in one dimension two probabilities, none of them necessarily related to (point) mutations. These probabilities are: the distribution of conformational probabilities of gene P and the probability of percolative motions displacing P from its frustrated position. (Frustration may conceal local spins as epigenetic or topologic determinants of clonally directed site and tissue specific mutations.)

A solution of the above equation reads:

$$\langle X_j^2 \rangle_t \cong t^{D_f}$$

Exponent D_f relates to fractal and intermittently percolative motions iterated by segment j within the space-time (4D) mass of co-moving strings (a caged, monstrous Peano curve or Menger sponge). D_f is expected to fluctuate around values much less than unity [3, 4]. Therefore, even a long period (t) of mitotic activity is bound to yield a narrow spectrum of discommensured mo-

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tions, thus reducing the probability that segment *j* will acquire a special conformation optimal for expressing *P*. Such a "unique"(?) conformation might occur most rarely within a population of cells, all initially stimulated and mitotically recruited by exogenous potential over extended times. The acquisition of autocatalytically synthesized potential is thus a rare event, expected to culminate clonally on top of the "Devil staircase" [5]. It is conjectured that all other mitosing cells dissipate exogenous potential in naive (nonexpressible) configurations of their chromatin segments, including *j*, with the exception of "almost" every other segment belonging to "ballistic or active layers" and imprinted by the genes of specific differentiation programs. The above conclusions are supported by the fact that only a small portion of the (human) genome encodes functionally active genes. The DNA bulk is often considered as a "useless ballast." However, by dynamic intermingling, such DNA traps many genes, including *P*, into innumerable entanglements greatly limiting changes in their (nonexpressible) conformations and accidental activation.

The complicated dynamics of disordered motions of concatenated strings within a finite space crowded by traps are being actively investigated. Additional information relevant to this paper is given in works on disordered-chaotic motions, Birkhoff signatures of tangles, classic-quantum multicollisional billiards, Krylov mixing, broken ergodicity, KAM (Kolmogoroff-Arnold-Moser) tori, their stability, Arnold's diffusion, etc. [6–10].

The very long, thin DNA is confined within finite nuclear subspaces. To fit into such small volumes, DNA must arrange many of its sections into looped configurations not too dissimilar, dynamically speaking, to the so-called KAM tori. While residing within such cages, gene *P* remains unexpressed because it is unable to modify its configuration and interact optimally with a suitable activating "matrix." Such a matrix may become available only at certain stages of differentiation. If so, the equation must include additional probabilities, none of them necessarily or sufficiently "mutational" in nature. These probabilities, coupled to those mentioned explicitly, further reduce the chance of *P* activation in dividing cells. However, the form of the solution is not appreciably affected.

After N mitoses, caging tori might become genequaked or "messed up," with the result that in some cell gene *P* is repositioned into a new hierarchy of configurations. Two of these are particularly interesting. If *P* drifts into the so-called stochastic diffusion layer (Arnold's web) before cell terminal differentiation, there is an increased probability of its activation, if a matrix is available. In that case, a most "unlucky" cell becomes marginally or sufficiently autonomous for self-renewal. This is a prerequisite for the appearance of a new state (malignancy) among those states mapped in the "field" of a normal cell, absolutely dependent from local microenvironmental sources. Alternatively, if located ultrametrically in some residual and/or continuously re-forming insular trap near the boundary of Arnold's web, for example, gene *P* should remain forever silent.

In addition to immune surveillance, the permanent caging of gene *P* is thus an efficient mechanism against cancer development during a substantial part or even the entire life span of many individuals, in spite of constant or sporadic exposure to carcinogens and "mutagens."

Finally, there is valuable information to be collected by studying the cell genome in toto rather than by simply linear DNA sequencing, e.g., degree of lacunarity, unfolding of chromatids (spongy rods with zero or *negative* Gaussian curvature), and their quantal and asymmetric wobbles around fragile scaffold (∓DNA) swivel points imposed by the bending energies of the nuclear envelope which contributes *positive* curvature during the cup-to-sphere transformation of the nucleus.

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