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[Xun Hu](#) *

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Concept Paper

The Biological Algorithm for Cancer Therapy

Xun Hu

Zhejiang University Cancer Institute; huxun@zju.edu.cn

Abstract

Modern cancer therapy is largely grounded in a linear paradigm in which drug–target interaction is assumed to be the dominant determinant of therapeutic outcome. Yet across virtually all tumor types and treatment modalities, clinical responses remain profoundly unpredictable: patients with nearly identical disease characteristics often exhibit radically different outcomes to the same therapy, and biomarker-positive tumors can be either exquisitely sensitive or entirely refractory. These inconsistencies expose fundamental limitations of a single-dimension, drug-centered framework and indicate the presence of deeper system-level determinants. Here, I introduce the concept of the high-dimensional biological algorithm—the nonlinear, multidimensional computational logic by which the tumor–host system integrates all internal and external variables to generate therapeutic outcomes. This algorithm is not mutable code but is embodied in the invariant laws and principles of physics, chemistry, and biology (such as biochemistry, biophysics, molecular biology, cell biology, immunology, physiology) in the tumor–host system. While these governing principles remain constant, the algorithm faithfully processes its inputs; thus, system output is determined entirely by the nature and configuration of those inputs. Within this framework, a drug is not a direct cause of outcome but one input among many entering a system that simultaneously processes biochemical, metabolic, signaling, immunological, structural, and microenvironmental variables. The quantities and qualities of these variables differ between patients, between tumors, within individual tumors, and over time. Consequently, when the same drug is introduced into tumor–host systems with different computational baselines, it enters fundamentally distinct input landscapes. Although processed by the same underlying algorithm, these differing baseline conditions necessarily drive computation along divergent trajectories, yielding heterogeneous therapeutic outcomes. Thus, variability in therapeutic response is not a failure of the drug nor a change in the governing biological algorithm, but a predictable consequence of applying identical inputs to heterogeneous computational baselines. Achieving consistent and durable therapeutic efficacy therefore requires reconditioning the baseline inputs presented to the algorithm, rather than attempting to modify the algorithm itself. A second-dimension input, distinct from molecular targeting, is therefore required to constrain or recondition the computational baseline through which the algorithm processes therapeutic inputs, thereby favoring convergent and therapeutically productive outputs. Concentrated bicarbonate provides a proof-of-concept example: by sharply alkalizing extracellular and intracellular pH, it reconditions global baseline parameters—including enzymatic kinetics, metabolic flux distribution, mitochondrial energetics, immune visibility, and signaling thresholds. In clinical studies, including bicarbonate-integrated TACE and bicarbonate-augmented anti-PD-1 therapy, this conditioning transformed previously variable responses into uniform, high-magnitude outcomes, despite unchanged drugs, doses, and delivery routes. Together, this framework suggests that future progress in oncology will require moving beyond an exclusive focus on drug–target interactions, toward strategies that combine molecular targeting therapies with deliberate manipulation of the computational baseline that governs how therapeutic inputs are interpreted and executed. Integrating pharmacology with system-level input conditioning offers a principled path toward more predictable, controllable, and robust cancer therapies.

Keywords: cancer therapy; biological algorithm; linear algorithm; second-dimension input

1. Modern Cancer Therapy as a Linear Algorithm

Modern cancer therapy is built upon one of the most successful scientific strategies of the past half-century (1,2): the identification of molecular abnormalities that drive malignant growth and the rational design of drugs to inhibit those abnormalities. This approach — commonly referred to as *precision oncology* — has transformed many aspects of cancer care.

Across tumors and organ systems, specific genetic mutations, overexpressed oncogenes, aberrant signaling pathways, and immune regulatory checkpoints have been identified and exploited as therapeutic targets. Tyrosine kinase inhibitors (TKIs), monoclonal antibodies, antibody–drug conjugates (ADCs), and immune checkpoint inhibitors (ICIs) exemplify the clinical power of this strategy. Many of these agents have produced unprecedented responses in certain patient populations and have extended survival in numerous malignancies.

At its conceptual core, modern cancer therapy follows a linear algorithm:

1. Identify a dominant molecular aberration, driver mutation, or pathogenic pathway.
2. Design or select a drug that specifically targets this abnormality.
3. Administer the drug.
4. Expect therapeutic efficacy to follow as a consequence of target inhibition.

In this framework, drug–target interaction is the dominant variable governing outcome. Therapeutic success is, therefore, assumed to scale with:

- the accuracy of target identification,
- the specificity and potency of the drug,
- and the efficiency with which the drug reaches its target.

Over the decades, the field has continuously refined this genetic and molecular targeting logic. From broadly cytotoxic chemotherapeutic agents such as anthracyclines, alkylating agents, and antimetabolites, oncology has advanced toward increasingly selective interventions: next-generation TKIs, highly engineered antibodies, and immune-modulatory biologics. Each successive innovation has strengthened the belief that improving drug design and expanding target specificity would ultimately solve the problem of cancer therapy.

Yet, despite this dramatic technological evolution, a persistent problem remains: therapeutic outcome is fundamentally unpredictable (3,4).

At the population level, even patients with nearly identical tumor type, stage, genetic mutation profile, and treatment regimen exhibit widely divergent outcomes—from complete remission to rapid progression. This variability persists across landmark settings: targeted therapies in breast and lung cancer, immune checkpoint blockade in melanoma and HCC, or systemic chemotherapy across solid tumors. These differences remain enormous even when therapy selection is guided by established biomarkers.

The field has acknowledged these inconsistencies using terms such as “tumor heterogeneity,” “host variability,” or “individual differences.” Yet within the linear drug-centered framework, these explanations remain incomplete. Increasing drug potency, combining more drugs, and refining biomarkers have improved outcomes only modestly, and rarely in predictable ways.

A second deeper contradiction arises at the level of individual tumors. Even when two tumors show *similar biomarker positivity*—for example, both meeting criteria for HER2-positive disease (IHC 3+), or both classified as PD-L1-positive by accepted scoring thresholds—their therapeutic responses can diverge completely. Some biomarker-positive tumors undergo complete eradication with targeted or immune-based therapies, while others exhibit minimal or no response. This inconsistency is further complicated by the fact that biomarker scoring typically reflects only a fraction of tumor cells under fixed criteria (e.g., ≥10% HER2 IHC 3+, ≥1% PD-L1 TPS), yet therapies can still induce whole-tumor regression. Conversely, some tumors that are similarly biomarker-positive remain entirely refractory. Taken together, these paradoxes cannot be explained by drug–target interaction alone. They reveal fundamental gaps in the linear assumption that target expression → drug binding → tumor eradication.

This limitation does not negate the importance of drugs or targets. Rather, it indicates that a critical dimension of the problem lies outside the current conceptual framework.

In the following section, I would move beyond this linear perspective to introduce a second, fundamentally different dimension of therapeutic determination: the biological algorithm — a complex, nonlinear system through which the tumor–host environment interprets and transforms all therapeutic inputs.

2. The Biological Algorithm in a Complex Tumor–Host System

The limitations of the linear drug-centered framework do not arise because the drugs themselves are inadequate, but because the framework overlooks the nature of the system in which these drugs must operate. A tumor does not exist as a simple target; it resides within a constantly changing, multidimensional biological environment. Every drug introduced into this environment immediately enters a vastly more complex computational landscape—one shaped by biochemical fluxes, signaling networks, immune dynamics, microenvironmental conditions, and structural tissue organization. To understand why therapeutic outcomes vary so widely, one must therefore shift focus from the linear logic of drug → target → effect to the underlying system that receives, interprets, and transforms all inputs. This underlying system operates according to what can be described as a **biological algorithm**.

The biological algorithm refers to the **invariant set of physical, chemical, and biological laws** through which a living system integrates, processes, and transforms all incoming inputs into a physiological output. Unlike an engineered algorithm written in code, this algorithm is embodied in the fundamental principles governing biological matter and energy.

Importantly, **the biological algorithm itself does not change**. It is defined by conserved rules, including but not limited to:

- biochemical kinetics and thermodynamics,
- principles of metabolic flux and energy balance,
- signaling network logic and feedback regulation,
- immunological recognition and activation thresholds,
- structural constraints imposed by tissue organization.

What varies—and what gives rise to divergent outcomes—is **the set of conditions and inputs under which this algorithm operates**.

In the tumor–host system, the biological algorithm continuously processes a vast array of simultaneous inputs, including but not limited to:

- drug exposure,
- biochemical reactions and metabolic network,
- intracellular and extracellular pH,
- nutrient and oxygen availability,
- redox state and energetic charge,
- signaling context and network topology,
- immune cell composition and activation state,
- stromal, vascular, and microenvironmental constraints.

The variables feeding into this algorithm are summarized in Table 1, noting that the true set of variables is innumerable and their combinations effectively infinite; the table only contains representative examples.

Table 1. The representative variables feeding into this algorithm.

System Layer	Representative Variables & Features
Biochemical / Enzymatic	• Biochemical reactions • Enzyme kinetics and thermodynamics

	• Substrate/product ratios • Reaction equilibria
Metabolic	• Metabolic flux distributions • Metabolic programming • ATP/ADP/AMP balance • Nutrient utilization patterns • Glycolysis–OXPHOS balance
Redox / Ionic	• Redox balance (NAD⁺/NADH, GSH/GSSG) • Reactive oxygen species (ROS) • Intracellular/extracellular ion gradients (Ca²⁺, Na⁺, K⁺, H⁺)
pH / Microenvironment	• Intracellular and extracellular pH • pH landscape across tissues • Lactic acidosis • Oxygen and nutrient availability
Organelle / Bioenergetic	• Mitochondrial function and bioenergetics • Organelle dynamics (mitochondria, lysosome, ER) • Membrane potential ($\Delta\Psi_m$)
Signaling	• Signaling cascades (PI3K/AKT, AMPK, MAPK, NFκB, etc.) • Adaptive signaling loops • Feedback and compensatory circuits
Gene / Epigenetic	• Gene expression patterns • Epigenetic configuration (DNA methylation, histone modification) • Transcriptional plasticity
Cellular State	• Proliferative capacity • Survival or death tendency • Resistance or sensitivity to stress • Internal cellular state
Immune / Inflammatory	• Immune surveillance • Immune cell composition • Immune tone and activation states • Immune visibility or evasion
Intercellular / Tissue	• Cell–cell communication • Stromal interactions • Vascular architecture • Extracellular matrix properties
System	• Signaling network topology • Compensatory networks • Adaptive dynamics • Tissue-level organization

This list is representative, not exhaustive.

These inputs define the initial conditions and boundary constraints of computation. Because these conditions differ between patients, between tumors within the same patient, and over time

within a single tumor, the same algorithm executes the same drug input under different computational regimes.

The biological algorithm operates through multiple interconnected layers—including biochemical, metabolic, signaling, immune, and microenvironmental domains—but the governing rules across these layers remain constant. The observed variability in therapeutic outcome therefore reflects **condition-dependent execution**.

Thus, the physiological state of cancer cells—the phenotype, the metabolic behavior, the degree of immune visibility, and the therapeutic response—is an output of this continuously operating algorithm.

3. Drug is an Input and the Output—Therapeutic Outcome—is Generated by the Biological Algorithm

Thus, the physiological state of cancer cells—including growth behavior, metabolic phenotype, immune visibility, stress tolerance, and response to therapy—is best understood as an **output generated by a fixed biological algorithm operating under heterogeneous conditions**.

This distinction is critical: therapeutic unpredictability does not arise because biology lacks rules, but because those rules are applied to vastly different and dynamically evolving input states.

If the tumor–host system operates through a multidimensional and nonlinear biological algorithm, then a crucial implication follows: no input—including a drug—acts alone or determines its own fate. Every therapeutic agent enters a system already with ongoing biochemical, metabolic, immunological, and microenvironmental inputs (Table 1). What emerges downstream is not the direct consequence of the drug’s molecular action, but the result of how the system integrates that drug into its internal computational logic.

Drug administration is therefore best understood not as a direct cause of therapeutic outcome, but as one input among many entering a biological algorithm. In parallel, all components of the tumor–host environment—including biochemical, metabolic, signaling, immunological, and structural factors (Table 1)—function as simultaneous inputs into this same algorithm.

The final therapeutic effect emerges only after these diverse inputs are integrated, interpreted, and transformed through a layered, nonlinear, and adaptive system. Because the values, configurations, and interactions of these variables differ between individuals, between tumors within the same individual, and even within the same tumor spatially and temporally, the algorithm processes the same drug input differently. This alone can account for the wide differences in therapeutic responses observed among patients with similar disease characteristics and mixed response.

Understanding cancer therapy thus requires a conceptual shift:

From

Drug → Outcome (linear, single-dimension model)

To

Input → Biological Algorithm → Outcome (nonlinear, multidimensional model)

4. Aligning the Computational Baseline with a Second-Dimension Input

Because the biological algorithm itself—the fundamental laws and principles of physics, chemistry, and biology governing how living systems integrate and process information—remains constant, therapeutic unpredictability cannot arise from variability in the algorithm. The algorithm faithfully receives inputs, processes them according to invariant rules, and generates outputs. Variability in therapeutic outcome must therefore originate from variability in the inputs presented to the algorithm, rather than from changes in the algorithm itself.

In each tumor–host system, the internal variables that constitute the computational baseline—including biochemical, metabolic, immunologic, and structural parameters (Table 1)—differ markedly in both quantity and quality. These variables function as simultaneous inputs that define

the initial conditions under which computation occurs. When the same drug is introduced into tumor–host systems with different computational baselines, it enters fundamentally different input landscapes. Although the biological algorithm processes all inputs according to the same underlying laws, differing baseline conditions necessarily drive computation along divergent trajectories. As a result, identical drug inputs are transformed into distinct system-level outputs, yielding widely variable therapeutic outcomes.

Thus, variability in response is not a failure of the drug, nor a change in the governing biological algorithm, but a predictable consequence of applying the same input to heterogeneous computational baselines. Achieving consistent and durable therapeutic responses therefore requires constraining or reconditioning the baseline inputs presented to the algorithm.

4.1. Computational Baseline Alignment

Computational baseline alignment does not require erasing biological diversity. Rather, it involves imposing a dominant, system-level constraint strong enough to override local network idiosyncrasies and reorganize variables in a coordinated manner.

The result is a shared physiological baseline—a set of global parameters under which the same drug input is more likely to be processed through comparable computational logic, producing more uniform therapeutic outputs. These parameters include, but are not limited to, intracellular and extracellular pH, redox balance, metabolic flux distribution, organelle functional status, signaling network tone, and thresholds governing antigen processing and immune activation. Importantly, these are not molecular “targets.” They are system-defining conditions that determine the operating domain of the biological algorithm.

Once these boundary conditions are aligned, the system behaves analogously to resetting distributed processors to a common boot state, synchronizing clocks in a multi-node computing network, or normalizing initial conditions before executing a complex computation. The drug itself is unchanged; what changes is the context in which the drug is computed. Predictability emerges not from further refinement of drug design alone, but from restoring coherence to the system’s computational baseline.

4.2. Aligning the Computational Baseline with a Second-Dimension Input

If the drug constitutes the first input into the therapeutic system, then achieving baseline alignment requires a second-dimension input—one that operates at a different conceptual level and reconfigures the global conditions under which the algorithm computes drug information. Unlike targeted therapies, which interact with defined molecular nodes, a second-dimension input modifies the conditions of computation themselves. By reshaping fundamental physicochemical parameters such as pH, ion gradients, redox balance, energetic state, membrane and mitochondrial potentials, and immune-activation thresholds, this second input exerts system-wide effects rather than acting within any single pathway.

Concentrated bicarbonate provides a clear experimental example of such a baseline-conditioning input. Direct intratumoral delivery of concentrated sodium bicarbonate induces a marked increase in both extracellular and intracellular pH, thereby altering one of the most globally influential physicochemical variables in biology. This pH shift initiates a sequential cascade of biochemical and signaling changes, including:

- modulation of catalytic rates of metabolic and signaling enzymes;
- alteration of thermodynamic feasibility of key reactions;
- changes in conformational states of pH-sensitive proteins;
- redistribution of phosphorylation equilibria;
- collapse of mitochondrial ΔpH and $\Delta\Psi\text{m}$ with disruption of proton-motive force;
- alkalization of lysosomes leading to blockade of autophagic flux;
- enhancement of antigen processing, MHC-I presentation, and immune visibility.

Because pH governs a vast array of intracellular and microenvironmental variables, its elevation forces metabolic, signaling, and immunologic networks toward a more convergent operating condition. Tumors that previously computed drug input through highly divergent baseline conditions now process the same input through a more uniform computational landscape, yielding convergent therapeutic outputs.

Our prior work empirically substantiates this reasoning. We demonstrated that lactic acidosis enforces a low-flux, energy-efficient metabolic mode supporting tumor survival under nutrient scarcity, and that bicarbonate abolishes this state, destabilizing metabolic homeostasis (5-9). We showed that alkalization collapses mitochondrial ΔpH and $\Delta\Psi_m$, disrupts OXPHOS, elevates AMP, activates AMPK-mediated autophagy, but ultimately blocks autophagic flux through lysosomal alkalization (10). We further demonstrated persistent opening of the mitochondrial permeability transition pore with mtDNA release and activation of the cGAS-STING/TBK1/IRF3 pathway, converting 'cold' tumors into immune-infiltrated ones (11). Finally, bicarbonate was shown to shift TNF- α signaling from prosurvival NF- κ B activation toward RIP1/RIP3/MLKL-mediated necroptosis.

Although these findings represent only a tiny fraction of the system-wide changes induced by baseline conditioning, together they demonstrate a multilayer recalibration of metabolism, signaling, and immune tone consistent with computational baseline alignment.

Once this baseline is aligned, the same drug input is interpreted through similar logic across tumors, therapeutic outputs become more reproducible, and the apparent heterogeneity of biological responses is substantially reduced:

Unaligned state:

(Drug + heterogeneous system variables) $\rightarrow$ divergent computation $\rightarrow$ unpredictable outcomes

Aligned state:

(Drug + baseline-conditioning input) $\rightarrow$ constrained computation $\rightarrow$ reproducible outcomes

This framework provides a mechanistic interpretation for why, in intratumoral alkalization studies such as bicarbonate-integrated TACE (12, 13) or bicarbonate-augmented anti-PD-1 therapy (11), drugs that previously yielded widely variable outcomes instead produced uniform, high-magnitude responses.

In this sense, concentrated bicarbonate represents an archetypal second-dimension baseline-conditioning input—one capable of constraining a biologically diverse system so that the same drug can finally be processed predictably and productively. It serves as proof-of-concept that conditioning the computational baseline is both feasible and therapeutically consequential.

5. Two Examples of Intratumoral Alkalization: Aligning the Computational baseline

The computational baseline alignment hypothesis is not purely conceptual. It is supported by two independent, clinically observed phenomena in hepatocellular carcinoma (HCC), in which intratumoral bicarbonate was locally delivered. These examples are particularly representative because the therapeutic drug itself remained unchanged and only the operating condition of the biological algorithm was altered.

5.1 Bicarbonate + TACE (TILA-TACE):

In conventional transarterial chemoembolization (cTACE), the chemotherapeutic agent and ischemic stress together constitute the dominant therapeutic inputs. However, clinical efficacy is highly variable: a comprehensive meta-analysis by Lencioni (14) summarized TACE outcomes across studies from 1980 to 2013, reporting an average objective response rate (ORR) of 52.5% and a median overall survival (OS) of 19.4 months. More recent studies have reported similar ORRs values ranging from 19.5% to 58% (15–18), confirming the moderate and highly variable efficacy of cTACE in clinical practice. This variability in efficacy is primarily attributed to the biological heterogeneity of HCC.

Tumor size, vascularity, metabolic characteristics, and molecular features all influence treatment response.

Within the framework proposed here, these outcomes are consistent with a cytotoxic computation occurring under an unfavorable baseline condition. In the acidic, metabolically constrained tumor microenvironment, ischemia and chemotherapy are often processed by the biological algorithm as stress signals to be tolerated and adapted to, rather than as instructions for irreversible cell death.

When 5% sodium bicarbonate was intermittently infused into tumors during TACE (bicarbonate-integrated TACE), while keeping all other procedural variables constant (same catheter system, same chemotherapeutic agent, same embolization strategy), the therapeutic output changed strikingly. Across a total cohort of 453 patients from 2 independent studies (12, 13) spanning early-, intermediate-, and advanced-stage HCC, with tumor sizes ranging from 0.5 cm to 20.5 cm, response rates increased dramatically and response heterogeneity largely disappeared.

Importantly, under bicarbonate-integrated TACE, therapeutic efficacy became largely independent of conventional biological heterogeneity—including tumor size, disease stage, and molecular subtype—and instead depended primarily on a technical determinant: the vascular architecture of the tumor and the operability of its feeding arteries. Objective response rates approached ~100%, and variability across patients, across tumors, within individual tumors, and across disease stages was markedly reduced. Treatment outcomes could be systematically categorized into four procedural patterns:

1. Complete clearance in a single session: when all tumor-feeding arteries were clearly visualized by DSA and technically accessible, complete tumor clearance was achieved in a single TILA-TACE procedure.
2. Sequential clearance due to initial arterial inoperability: if all feeding arteries were identified but some were initially too small for catheterization, partial clearance occurred during the first session. Residual tumor tissue was subsequently eradicated once arterial dilation permitted catheter access.
3. Delayed clearance after identification of initially missed arteries: In cases where some feeding arteries were not visualized during the initial DSA, partial treatment resulted. Subsequent angiography identified these vessels, allowing complete clearance in follow-up sessions.
4. Partial clearance in tumors only occurs in those tumors with residual regions inaccessible to catheter-based delivery.

Overall, the complete response rate increased to over 70%. Residual disease, when present, was attributable not to tumor biology but to technical limitations in arterial access. In practical terms, when tumor-feeding arteries were operable, complete response rates approached ~100%, regardless of tumor size or disease stage.

Critically, the only methodological change introduced was the alteration of intratumoral pH.

From a computational perspective, bicarbonate reconditioned the baseline inputs—specifically the physicochemical environment—under which the unchanged biological algorithm processed ischemia and chemotherapy. Under this reconditioned baseline, the same cytotoxic inputs were no longer interpreted as survivable stress but were computed as lethal signals, resulting in uniform and decisive tumor destruction.

This clinical phenomenon provides a direct demonstration that therapeutic failure in cTACE arises not from insufficient therapeutic potency, but from unfavorable baseline conditions under which the biological algorithm operates. Reconditioning these baseline inputs transforms the system's computation and, consequently, its therapeutic output.

5.2 Bicarbonate + Anti-PD-1: Aligning an Immunological Algorithm

Anti-PD-1 antibodies act at the molecular level to release exhausted T cells from inhibitory signaling. Yet in hepatocellular carcinoma (HCC), landmark trials reported objective response rates (ORRs) of 15–20% (19,20). This limitation does not arise because PD-1 blockade is intrinsically

ineffective, but because the immunological branch of the biological algorithm is operating within an immunosuppressive computational state. Under such conditions, even an optimally designed immune checkpoint inhibitor cannot be processed through a productive immunological logic.

When concentrated bicarbonate was administered intratumorally alongside anti-PD-1 therapy, the therapeutic landscape changed markedly. In a prospective pilot study of 30 HCC patients (28 advanced-stage, 2 intermediate-stage HCC), this combination achieved a 93.3% objective response rate and a 53.3% complete response rate (11).

Yet nothing about the drug changed, same antibody, same dose, same pharmacokinetics, same route of administration. Only the algorithmic condition changed. Alkalization induced by bicarbonate exerted system-level effects that reconfigured how the immunological algorithm processed PD-1 blockade, including relieving suppression of antigen processing and immune signaling; enhancing MHC-I antigen presentation on tumor cells; increasing immune-cell infiltration into the tumor microenvironment; improving T-cell metabolic fitness and effector function.

From an algorithmic perspective, bicarbonate unlocked the immune-processing branch of the tumor-host system, allowing PD-1 blockade to be interpreted and executed through a more favorable computational state. This suggests a broader principle: immunotherapy often fails not because the drug is weak, but because the computational baseline is misaligned to the immunological incompetent direction. When the baseline is aligned, the same drug proceeds to immunological competent state.

6. Outlook

The framework in this paper proposes that cancer therapy does not operate solely within a single linear dimension defined by drug–target interactions, but within a high-dimensional biological algorithm that governs how all therapeutic inputs are interpreted and executed. This reframing provides a coherent conceptual basis for long-standing paradoxes in oncology, including heterogeneous outcomes among clinically similar patients, mixed responses within the same individual, and inconsistencies in biomarker-guided therapies. Importantly, it does not diminish the central role of molecular targeting; rather, it explains why molecular targeting alone is often insufficient to produce predictable outcomes.

By recognizing therapy as Input → Biological Algorithm → Output, treatment variability is no longer viewed as stochastic noise or unexplained heterogeneity. Instead, it emerges as a predictable consequence of introducing the same drug input into tumor–host systems with different computational baselines. While the governing laws and principles of physics, chemistry, and biology—the biological algorithm itself—remain constant, the internal variables presented to that algorithm differ across patients, tumors, and time. These differences shape the computational trajectory through which a drug is processed, giving rise to divergent therapeutic outputs.

This perspective also offers an interpretation for why intensifying drug potency, adding more agents, or refining biomarkers—although sometimes increasing response rates (for example, from 20% to 40%)—often fail to resolve deeper problems such as heterogeneous responses within the same patient or paradoxical outcomes in biomarker-matched tumors. These strategies operate primarily within the linear molecular-targeting dimension and therefore do not constrain the broader computational landscape that ultimately determines outcome.

At the same time, the framework identifies a new and complementary avenue for therapeutic innovation: **conditioning the computational baseline under which molecular targeting operates.** The demonstration that intratumoral alkalization can globally reconfigure metabolic, signaling, and immunological conditions—and thereby allow existing drugs to achieve highly reproducible and markedly enhanced efficacy—provides proof-of-concept that therapeutic predictability can be improved without altering the drug itself. In this context, a second-dimension input does not replace molecular targeting but enables it, by shaping the system-wide conditions that determine how targeting information is processed.

The central challenge ahead is to define, discover, and systematically manipulate those global parameters that most strongly influence biological computation—such as physicochemical constraints, energetic states, and immune thresholds—while preserving physiological integrity. Addressing this challenge will require coordinated efforts across biophysics, metabolism, immunology, systems biology, oncology, and computational science.

Ultimately, this framework invites the field to confront a question at a different conceptual dimension: **How can we shape the system so that therapy can work?** This marks the beginning of a broader inquiry into the high-dimensional nature of biological computation in cancer and its therapeutic implications—one that aims not only molecular targeting, but also render it more predictable, controllable, and effective.

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