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A Review of Mathematical Models of Metastatic Cancer

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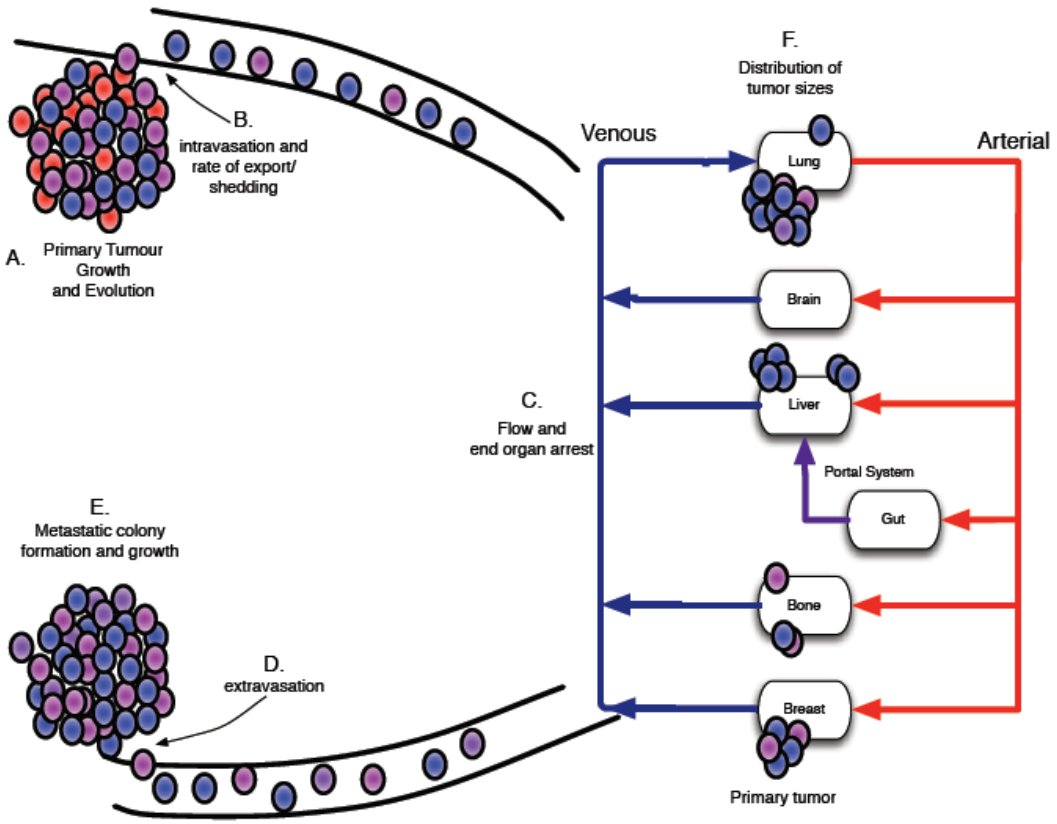
I. Introduction: The metastatic process of cancer

When cancer cells detach from an original tumor site to spread throughout the body, it is called metastasis. Metastatic cancer cells can move either by direct contact with new organ sites or through the blood or lymphatic systems of the body, but there is a generally accepted path process for this spread (1). First, the cells invade healthy tissue close to the original cancerous site, most likely by lymph or blood vessels—this is called intravasation (3). Once they are in one of these circulatory systems, the cancer cells travel to distant parts of the body. They stop in small blood vessels called capillaries where they traverse through the vessel walls and into surrounding tissues through a process called extravasation. The cells reproduce to develop small micrometastatic tumors. If the small tumor is able to stimulate growth of new blood vessels to attain a blood supply, the tumor can grow larger into a full-fledged metastatic tumor. Thriving metastases are also contingent on the properties of the noncancerous cells, such as immune system cells at the original and new sites as well as ones they encounter on their journey through the body (1). While it is believed that all types of cancer are able to spread metastatically, not every singular cancer cell has the ability to metastasize on its own. The most common sites of metastasis for all cancers (excluding lymph nodes since they are a method of transit for the cells) are the bone, liver, and lungs (1). The diagram below shows how cancer will spread from any original tumor site to various metastatic growth sites in the body.



An overview of the metastatic process (3)

It is important to note that even after the cancer has established a metastatic tumor in a new area of the body, the cancer itself is still the original type of cancer. For example, if cancer of the lung grows in the breast, the new tumor is still lung cancer that happens to have grown in the breast. The new cancer often has similar molecular features and causes the same protein and chromosome changes as the original (1).

It is possible for cancer to metastasize and lie dormant for years or even forever without growing enough to show symptoms of cancer at the new site. Since all types of cancer are susceptible to metastasis, experts have been working for decades to develop mathematical models to show the likelihood of metastasis in different locations of the body for all types of cancer. Creating a general model of metastasis has proven to be very difficult because cancer is a multifaceted process dependent upon a variety of cellular and micro-environmental parameters (11). Cellular parameters include "altered rates of cell proliferation, apoptosis [programmed cell death (15)], migration, adhesion, metabolism and mutation" (11). Micro-environmental constraints consist of "extracellular matrix composition,

angiogenesis [development of new blood vessels (15)], inflammation and proteases ["enzymes that catalyze the splitting of proteins into smaller peptide fractions and amino acids by a process known as proteolysis" (15)]". The most common methods of modeling are the use of Markov Chains, or partial differential equations, to determine the probability of different metastatic scenarios for different kinds of cancer. While some studies focus on cancer in general and others focus on specific cancer types, each study is useful since the process of metastasis is believed to be virtually the same for all cancers, even though the sites change from type to type. This paper will summarize five existing models and evaluate their dissimilarities to determine the best course of action in predicting metastasis in several types of cancer.

II. Models of Metastatic Cancer

A. Markov Chains

Newton et al. (8) took a Markov approach to identify the timeline and design of metastatic spread. They focused on lung cancer alone to gain a better understanding of the exact process of how the cancer cells reproduce and spread from the lungs to other parts of the body (3). Through their model, they showed that metastatic cancer is multi-directional, not unidirectional as many studies originally believed (8). The traditional "seed and soil" view was that circulating tumor cells (CTCs) are responsible for the spread by detaching from the primary tumor and traveling through the bloodstream and lymphatic system to new organs where, if conditions are favorable, they are able to reproduce and induce tumor growth. This model was unidirectional in that the CTCs travel from the primary to the new site only and do not return to the primary. Newton et al. cited more recent studies that had introduced the idea of "self-seeding", where CTCs that have left the primary site return and begin reproducing again. They also suggested that metastatic self-seeding ("metastasis from metastases") may even be possible. In their study, the authors defined three general classes of the cancer progression: self-seeding of the primary tumor, reseeding of the primary tumor from a metastatic site, and reseeding of metastatic tumors (8).

Newton et al. began by developing a network of organs susceptible to the cancer and assumed that any organ could receive the cancer from any other organ in the chain. Since they were using the data from autopsy results after long-term progression of the disease, they started the study already

knowing the final steady-state vector that would normally be found after many iterations of the transitional matrix. They then used an iterative Monte Carlo method—one that generates random numbers and observes the fraction of the numbers that obey a property or properties (14)—to solve for the probabilities of cancer cell transition between each organ to find the original P transitional matrix. They applied a discrete Markov chain system to this P matrix to determine the probabilities of different metastatic routes. From this data, they developed the diagram below to show how the cancer can spread from the lungs. The innermost ring consists of "first-order" sites, ones in direct contact with the lungs, starting with the most probable first step of metastasis (regional lymph nodes) at 12:00 with probability decreasing clockwise around the circle to the least likely first step of metastasis (skeletal muscle). The outer ring consists of "second-order" sites, ones where, for cancer to metastasize, it usually must first pass through a first-order site (8). Their diagram accounts for the multi-directional steps that allow the cancer to feed back into the lung or any metastatic site with arrows directed back toward those sites. Overall, they identified 756 possible two-step paths. They defined the strongest metastasis re-seeders as lymph nodes, followed by liver, adrenal bone, and kidney (8). They did a convergence analysis of their algorithm against the data set and noted that the only non-convergence occurred when they eliminated any possibility of primary metastasis or metastatic re-seeding and made the model uni-directional. However, when all connections in the diagram were allowed, the algorithm converged to a solution and produced a transitional matrix with many connections from site to site. They noted that after two iterations of their Markov chain, the state-vector had almost converged to the steady-state vector for metastatic tumors, effectively showing that lung cancer metastasis is a two-step process (8).

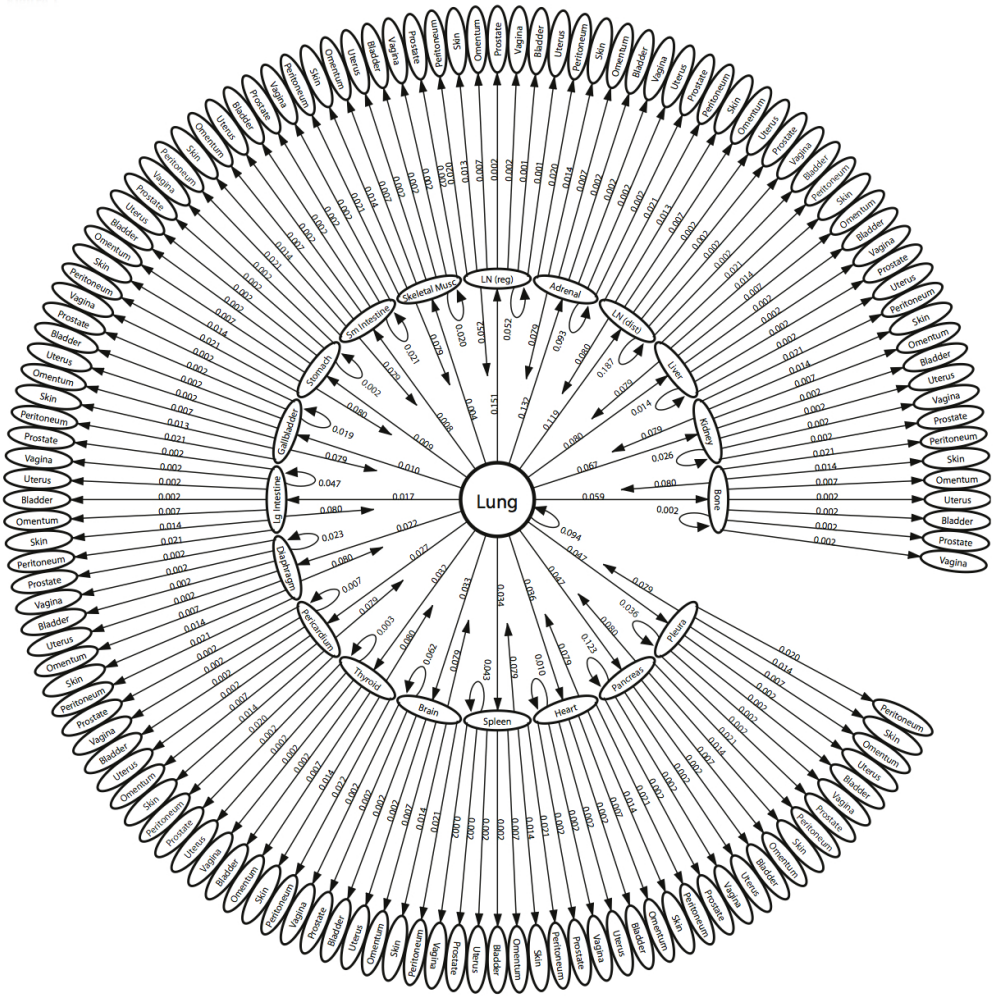
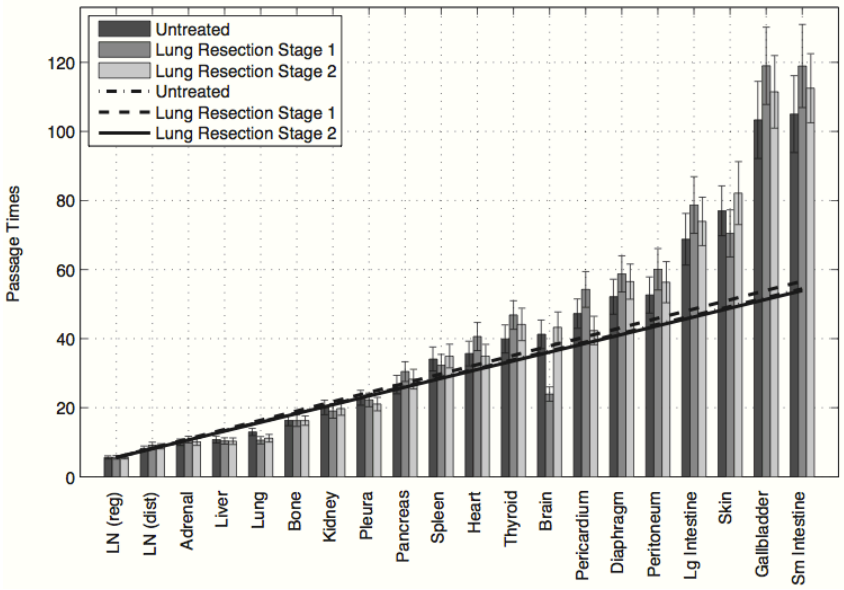


Diagram of metastatic spread of cancer from the lungs (8)

Through their study, Newton et al. were able to identify sites as either contributors to metastatic spread or as absorbing states by comparing the probability of cancer cell movement out of the site (P_{out}) over the probability into the site (P_{in}) (8). They defined "spreaders" like the adrenal gland and kidney as sites where $P_{out} > P_{in}$, meaning that if the cancer came to those organs it would likely be dispersed to other organs as well. Contrarily, they called sites like regional lymph nodes, the liver, and bone "sponges", where $P_{in} > P_{out}$, implying that the cancer would be limited to these locations instead of traveling and metastasizing elsewhere in the body. Their study included a graph of time-progression of the cancer through the different metastasis sites. While a patient's doctor may not be able to definitively predict the location of his or her cancer's first metastasis, this graph would be helpful in determining the timeline and future progression of the cancer once the first site is known. The graph can also be used to suggest treatment

methods of a specific cancer progression, especially whether resections at certain sites would be helpful or of no significant benefit to the patient.



Timeline of Lung Cancer Progression and Treatment (8)

Liotta et al. also used a Markov approach, but instead of only studying the movement of single CTCs, they considered that cancer cells travel in masses of assorted size (2). Their model consists of three types of tumor clumps: "tumor cell clumps in the circulation, tumor cells clumps arrested in the pulmonary capillary bed, and pulmonary metastatic foci" (2). They used their experimental data to base their study on the assumptions that clump death rate is inversely proportional to its size, that colonization rate is linearly correlated with clump size, and that the entry rate of clumps depends on size and follows a decaying power-law. They defined their overall objective as being to "provide a framework for predicting the development of metastatic foci from clumps in the pulmonary vessels and the probability of no metastatic foci existing after tumor initiation" (14).

Liotta et al. developed a two-dimensional Markov process to determine the probability of the population sizes of metastatic foci and tumor cell clumps at any time (14). The first state involves cancer cells penetrating the tumor wall to become exposed on the inner vessel surface. Once they are exposed, the tumor cells enter the blood circulation in clumps of varying size. Liotta et al. determined that clumps of four cells or greater would progress in the pulmonary blood vessels, but that smaller clumps and singular cells would adhere to the inner layer of the vessel and stop moving. They established that death of cell clumps could occur due to a variety of causes and created a probability equation to account for these reasons, which

included “destruction by host defense, removal from the pulmonary vessels, aging factors, or sheer stress damage” (14). This equation did not account for the loss of tumor cell clumps that had transformed into metastatic foci; they instead established a separate equation for the formation rate of metastatic foci from a tumor clump. They found that there is a direct correlation between the number of cancer cells that enter the bloodstream and the subsequent number of pulmonary metastases. They also determined that if cell clumps are larger, there is a greater number of resulting metastases, even if the overall number of cells entering the circulatory system is the same. They noted that in cancer cases, their model for the survival of cancer cells in the bloodstream might have significance in the prognostic process of a metastatic cancer (14).

Divoli et al. (5) also utilized a Markov approach, but instead of basing their study solely on raw data or experiments, they also interviewed 28 experts in different medical disciplines (breast, prostate, gastrointestinal, genetics, etc.). In these interviews, they requested a personal definition of metastasis from each interviewee and attempted to gain insight on the experts’ answers to key questions: “When do cells acquire metastatic abilities? What is the basis and importance of tropism [‘an involuntary orienting response; positive or negative reaction to a stimulus source’ (15)]? What (If any) is the relationship between metastasis, development and evolution?” (5). They analyzed the results in two ways. First, they used a chi-squared statistic to determine disparities in answers across the question topics and the difference in interest of each topic between the expert groups. Then they quantified similarity and dissimilarity between pairs of experts by employing a metric that corresponded each stage of metastasis with a letter to determine each expert’s thoughts on the chain of metastasis and then comparing his or her chain with another expert to determine the level of similarity (S_{ij}) or dissimilarity (D_{ij}). They defined similarity as “twice the number of ordered pairs common to the two sets” where $S_{ij} = S_{ii} + S_{jj}$ (15). They defined dissimilarity as “similarity minus the sum of all unmatched pairs of event from the two sets,” where $D_{ij} = S_{ii} + S_{jj} – 2\ S_{ij}$. They were able to create a set of quantitative data to use in a Markov Chain process to determine each expert’s opinion of the sequence of events in metastasis and create a standard to measure future experimental and observational data against (15).

To begin their Markov calculations, they created a transitional matrix P to represent each expert’s proposed path of metastasis with each entry of the matrix P_{ij} representing the probability of transition from state i to state j. They assumed each metastatic stage would depend only on the one directly

before, that transitional probabilities from one state to another would not change across the sequence, and that the cancer would not transition to itself. They defined N=28 possible states within the metastatic path (one from each expert), with each path starting at a state S and ending at a state E, and found that always ending the chain at stage E results in a steady state distribution vector of $\pi = (0,0,\ldots,1)$ defined by the distribution of transition probabilities using a Dirichlet distribution:

$$\{\rho_{ij}\}_{i\neq j;i>0;j=1,\ldots N} \sim \text{Dirichlet}\left(\frac{\alpha}{N-2},\ldots,\frac{\alpha}{N-2}\right).$$

$$f(\rho_{i1},\ldots,\rho_{iN}|\alpha) = \frac{\Gamma(\alpha)}{\prod_{j=1}^{N}\Gamma[\frac{\alpha}{N-2}]}\prod_{k=1}^{N-1}\rho_{ik}^{\frac{\alpha}{N}-1}.|$$

assuming $\alpha \geq N$-2. They also determined that the posterior distribution for p_{ij} was a conjugate Dirichlet distribution:

$$\{\rho_{ij}\}_{j=1,\ldots,N} \sim \text{Dirichlet}\left(\frac{\alpha}{N-2}+c_{i1},\ldots,\frac{\alpha}{N-2}+c_{iN}\right).$$

with the posterior expectation estimate of p_{ij} given by

$$\hat{\rho}_{ij}^{\ PE} = \frac{c_{ij}+\frac{\alpha}{N-2}}{C_i+\alpha}.$$

and a maximum a posteriori estimate of p_{ij} of

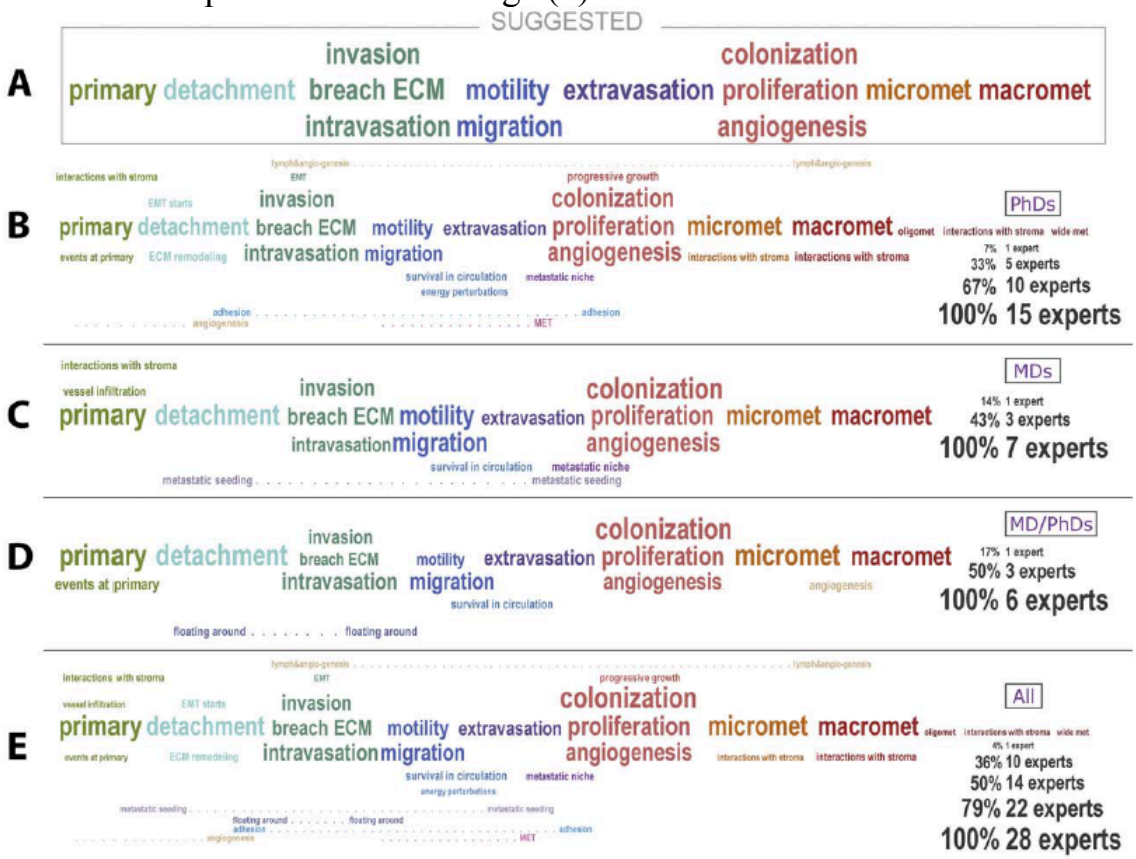
$$\hat{\rho}_{ij}^{MAP} = \frac{c_{ij}+\frac{\alpha}{N-2}-1}{C_i+\alpha-N+2},$$
$$\alpha \geq N-2,$$
$$i \neq j, j > 0.$$

where $\{c_{ij}\}$ is the set of observed counts of metastasis transition from all experts and

$$\sum_{j=1}^{N} c_{ij} = C_i.$$

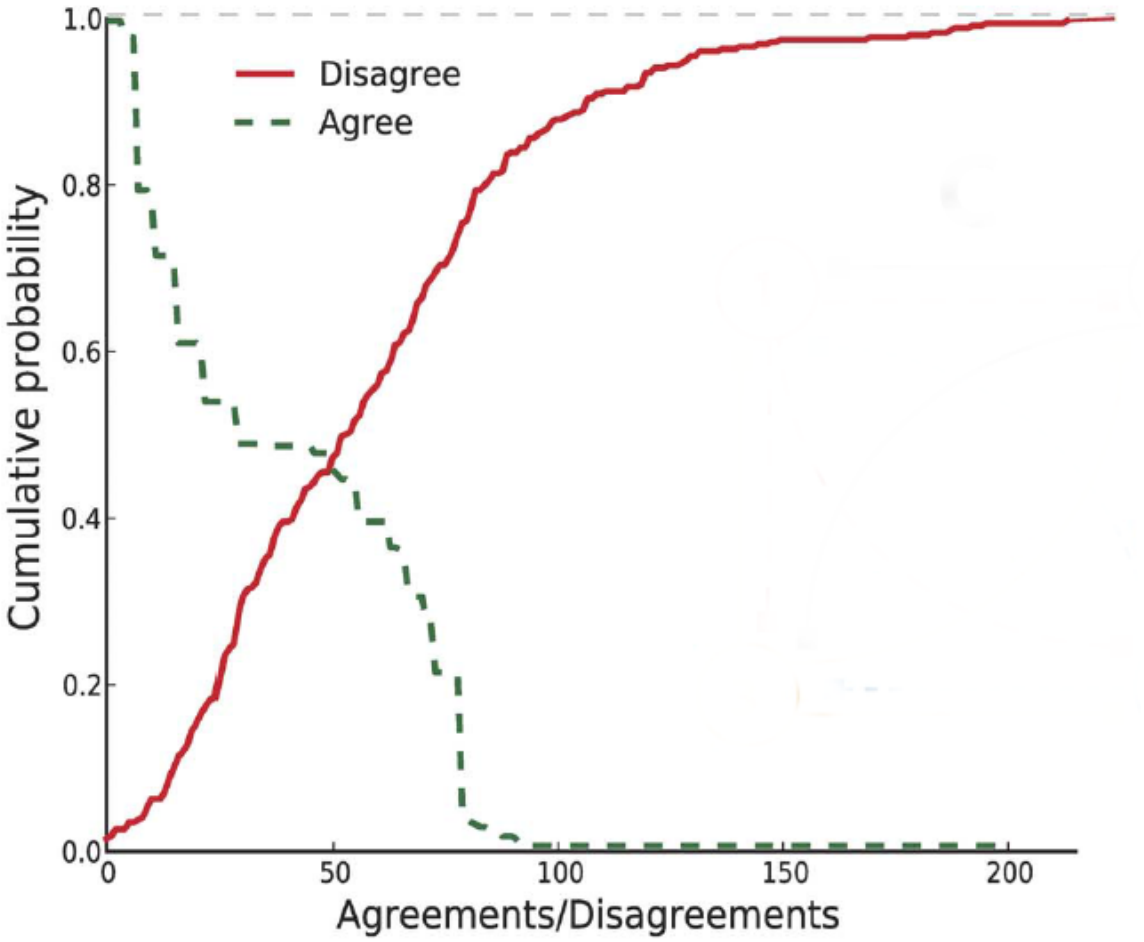
During the interviews, Divoli et al. (5) presented each expert with a supposed belief of the metastatic process that was purposely confused, expecting corrections and revisions. The experts would then suggest additions, deletions, and changes in the sequencing, which is shown in the diagram below. Overall, all experts agreed on the significant events

throughout the process, but not on the exact path of progression. They did, however, describe the steps in similar ways and, for the most part, agreed on the relative importance of each stage (5).



Visualization of expert views about the important stages of metastasis (9)

Since there was a significant disparity in how each expert considered the metastatic process, the team introduced a metric to compare two series of elements (two experts' descriptions) to determine the probability of any random pair of experts agreeing or disagreeing on at least *k* statements (5). They noted that the probability of agreement quickly dropped with *k* increasing while the probability of disagreement grew more gradually, which is shown in the graph below.



Quantifying the agreement between expert scenarios of metastasis (9)

In the conclusion of their study, Divoli et al. noted that the results they found were much more diverse and disconnected than they were expecting (5). The team anticipated some disparity in the experts' opinions of the smaller details but thought they would agree on the larger, more important aspects of the process. However, each expert's interpretation of metastasis was distinctly different from the rest. The amount of disproportion in the results reinforces the notion that metastasis is an extremely complex process with many different factors and possible paths. The Markov model that Divoli et al. presented is a first step and incentive to continue further research and development of a standardized consensus to gauge individual cancer progression so that clinicians will be able to better predict how metastasis will progress in every case.

B. Partial Differential Equations

Ramis-Conde et al. (9) focused their study of metastasis development not on the stages or chain of cancer cell movement, but on how the CTCs are able to leave the original tumor to migrate to other organs and tissues. They acknowledged that it is first necessary for the cancerous cells to penetrate the extracellular matrix (ECM) of the original site in order to invade surrounding tissue or enter the blood stream or lymphatic system to move throughout the body. They noted that the cancer cells must have the capability to produce reactions that would allow them to travel through the ECM, which would require degradation of the ECM. Therefore, they developed a hybrid model using partial differential equations that incorporated the interactions of individual cells with the ECM as well as the interactions of cells with each other.

The first part of their model assumes that the process of migration of a CTC through the ECM is triggered by contact between the ECM and the cell (9). When a cancer cell touches the ECM, it releases matrix metalloproteinases (MMPs) to degrade it. They defined the following equations:

$$\frac{\partial}{\partial t}E(\underline{x},t) = \underbrace{\lambda N(\underline{x},t)M(\underline{x},t)}_{1} + \chi_a \Delta E(\underline{x},t) - \mu_e E(\underline{x},t),$$

$$\frac{\partial}{\partial t}M(\underline{x},t) = -\beta E(\underline{x},t)M(\underline{x},t),$$

$$\frac{\partial}{\partial t}A(\underline{x},t) = \gamma E(\underline{x},t)M(\underline{x},t) + \chi_a \Delta A(\underline{x},t) - \mu_a A(\underline{x},t),$$

where M is the density of the ECM, E is the concentration of the MMPs, and A is the resulting density of the degraded ECM, which stimulates sells to migrate through the ECM. The tumor cell size N at a time t in a neighborhood of $\underline{x}$ is defined by

$$N(\underline{x},t) = \sum_{i=1}^{i=N} I_{B_\epsilon(\underline{x})}(\underline{x_i})$$

where $I_{B\varepsilon(x)}(\underline{x_i})$ is a heavyside function

$$I_{B_\epsilon(\underline{x})} = \begin{cases} 1 & \text{if } \underline{x_i} \in B_\epsilon(\underline{x}) \\ 0 & \text{Otherwise} \end{cases}$$

and $B\varepsilon(\underline{x})$ is the ball of radius ε, centered at $\underline{x}$. $\underline{Xi}$ is the position of the ith cell. 1 refers to the immediate production of enzymes by the cells within that radius, meaning that production is non-existent (0) if it is outside of the radius. They incorporated the interactions between cells in this model by assuming they would interact via the potential function below if their distance apart is less than ε, which they standardized as twice the size of the average cancer cell. The potential energy V between two cells at a time t is given by

$$V(\underline{x_i}, t) = I_{B_\epsilon(\underline{x_i})}\left(\frac{1}{d(\underline{x_i}, \underline{x_j}) + e_\infty} - he^{-(d(\underline{x_i},\underline{x_j})-\frac{\epsilon}{2})^2}\right)$$

where d is the distance, h is the capacity to bond, and e_∞ is the maximum possible energy. They represented the bonds connecting a set of cells greater than two as

$$V(\underline{x_i}, t) = \sum_{\underline{x_j} \in B_\epsilon(\underline{x_i})} \frac{1}{d(\underline{x_i}, \underline{x_j}) + e_\infty} - he^{-(d(\underline{x_i},\underline{x_j})-\frac{\epsilon}{2})^2},$$

where $B\varepsilon(\underline{xi})$ is a neighborhood with center $\underline{x_i}$ and radius of the maximum intercellular distance of ε. They assumed that cells would move closer to minimize the potential function between them at a constant speed, defining the direction of the cells movement (D) as

$$D = \overbrace{\nabla(-V(\underline{x}, t))}^{\text{direction driven by the potential}} + \overbrace{r\nabla A(\underline{x}, t)}^{\text{Direction driven by chemotactic gradient}}$$

where r indicates the cells' sensitivity to the chemoattractants—properties that incite cells to interact with each other.

As they proceeded in their study, Ramis-Conde et al. realized that they could drop off their original equation for $\partial/\partial t\ E(\underline{x},t)$ once they found evidence that the matrix degradation was confined to the areas of the ECM in contact with cells, and that the degradation process could be quantified without requiring the knowledge of the concentration of the MMPs. They considered the more straightforward system

$$\frac{\partial}{\partial t}M(x,t) = -\beta M(x,t)N(x,t),$$

$$\frac{\partial}{\partial t}A(x,t) = \gamma M(x,t)N(x,t) + \chi_a \Delta A(x,t) - \mu_a A(x,t),$$

which they solved to determine that the ECM is defined by

$$M(x,t) = e^{-\beta t} I_{[x_o-\epsilon, x_o+\epsilon]} + I_{\overline{[x_o-\epsilon, x_o+\epsilon]}},$$

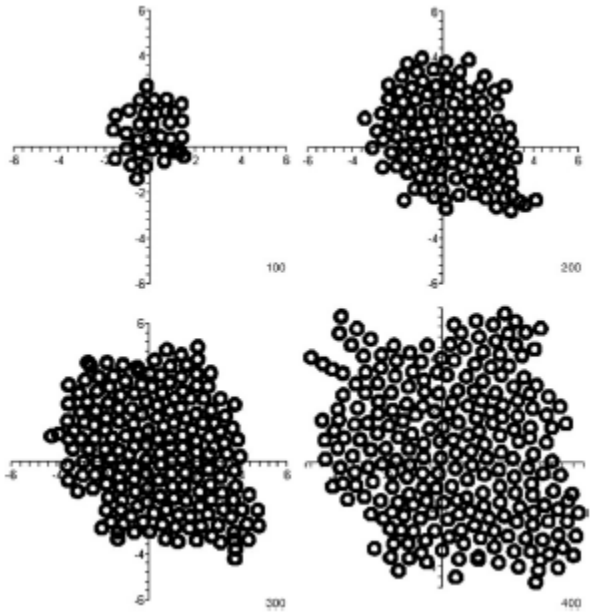
and the density of the degraded ECM by an individual cell is given by

$$A(x,t) = \sum_{n=1}^{n=\infty} \left[\frac{2\gamma \cos\left(\frac{n\pi x}{l}\right) \Big|_{x_o-\epsilon}^{x_o+\epsilon} (e^{-\beta t} - e^{-(\chi_a(\frac{n\pi}{l})^2+\mu)t})}{n\pi(\chi_a\left(\frac{n\pi}{l}\right)^2 + \mu - \beta)} \sin\left(\frac{n\pi x}{l}\right) \right],$$

taking into account the chemoattractants it is simultaneously releasing.

While they began their study hoping to demonstrate how one cell degrades the ECM and contributes to cancer spread, they ultimately realized that the degradation of ECM is positively correlated to heightened interactions between cells, as shown by the diagram below. Even when treating cells as individual entities, the chemoattractant gradients of those cells are extremely important in the invasion process.

Ao et al. (7) assumed that cancer progression is a stochastic process that can unintentionally transition cells from one stable tumor site to another, so cancer can spread unexpectedly and drastically even if it has remained in one spot for an extended period of time. They aimed to determine the cancer's endogenous network by mapping the pathways and modules that



Plots of evolution of cancer cells as they invade the ECM (9)

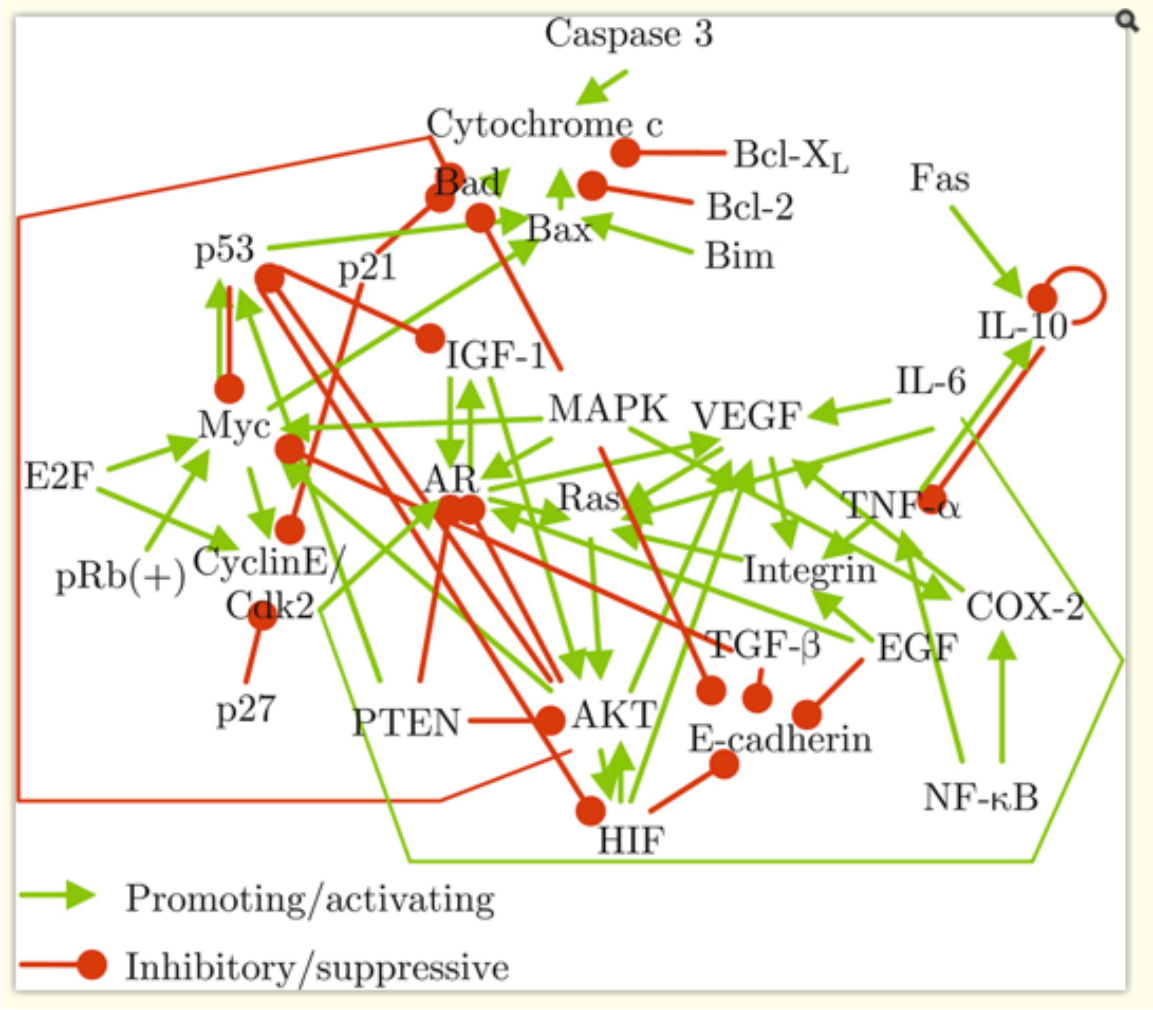
the cancer and other molecular and cellular agents may develop. They hypothesized that there is at least one level of virtually independent interaction between genetic and environmental factors that would allow one to map the spread of a cancer.

Ao *et al*. began by establishing the interactions between endogenous agents—ones that contribute to cancer growth in the body—and the enzymes

that activate or inhibit those agents from spreading through the body (7). They focused their study on prostate cancer, which is denoted by the occurrence of androgen receptor (AR) and the insulin-like growth factor receptor (IGF-1R) in the table below.

Endogenous agent	Activated by	Inhibited by
Cyclin E/Cdk2	Myc, E2F	p21, p27
Myc	pRb(+), E2F, Akt, MAPK	P53, TGF-β
p53	Myc, PTEN	Akt
Cytochrome c	Caspase 3, Bad, Bax	Bcl-2, Bcl-xL
Bad		p21, Akt, MAPK
Bax	Myc, p53, Bim	
Ras	VEGF, IL-6, Integrin, Androgen R	
Akt	NF-κB, HIF, Ras, IGF-1R	PTEN
VEGF	Akt, HIF, COX-2, IL-6, Androgen R	
IGF-1R	Androgen R	p53
Androgen R(AR)	EGF, IL-6	PTEN
Integrin	EGF, TNF-α, VEGF	
E-cadherin		TNF-α, EGF, HIF, TGF-β
HIF	Akt	p53
TNF-α	NF-κB	IL-10
IL-10	TNF-α, Fas	IL-10
COX-2	NF-κB, MAPK	

Table of interactions among cancer agents from targeted pair-wise experimental data (7)



Directed graph representation of the interactions from the table above (7)

They then formed an equation to represent the set of stochastic dynamics found in this network: $dx/dt = f(x) - x/r + \varepsilon(x,t)$, which shows that the deterministic force f can be modeled as sigmoidal (s-shaped) functions between 0 and 1 (7). They also defined the equations for activation, $f_A(y) = ay^n/(1 + ay^n)$, and inhibition, $f_I(y) = 1\text{-}f_A(y) = 1/(1 + ay^n)$, where the variables are normalized to the values $a = 10$ and $n = 3$ and the degradation time r is constant. They modeled this using a diffusion matrix D that they chose to be diagonal to simplify the calculations.

Ao et al. assumed that there would be multiple stable states and therefore there would be 3 possible outcomes of interactions with endogenous agents: states that parallel the healthy ones under normal conditions, stressful states that may lead to tumor growth, and ones in the tumor growth phase (7). The values in the table below are given in terms of their maximum activity.

	Normal growth	"Mountain pass"	Tumor-like state
Cytochrome c	0.08	0.01	0
Myc	0.84	0.60	0.53
CyclinE/CDK2	0.92	0.80	0.84
p53	0.16	0.05	0.01
Bad	0.26	0.11	0.06
Bax	0.29	0.10	0.07
Akt	0.02	0.37	0.63
HIF	0.00	0.34	0.72
TNF-α	0.16	0.37	0.44
Ras	0.18	0.73	0.81
COX-2	0.26	0.66	0.74
VEGF	0.19	0.83	0.93
IL-10	0.04	0.28	0.34
Integrin	0.39	0.57	0.65
Androgen R	0.13	0.36	0.54
IGF-1R	0.02	0.31	0.61
E-Cadherin	0.36	0.15	0.07

Table showing endogenous agent activity in 3 possible states of cancer growth (7)

Ao et al. stressed the need for a minimum amount of endogenous agents (37 in their model for prostate cancer) in order for cancer to spread. They noted that the table of activity above indicates that there is a limited probability that cancer will occur spontaneously, even without mutations or other debilitating factors, and that with further experimental observation, a more accurate quantitative model of cancer genesis and progression using endogenous agents is possible (7).

III. Evaluation: Disadvantages

There are aspects of each of these studies that can be helpful in future prognoses of cancer, but there are also many disadvantages. The studies by Newton et al. (8) and Ao et al. (7) considered only specific types of cancer: lung and prostate, respectively. While both studies presented a rough network of CTCs in the body, one can't assume that the pathways they discovered would be applicable to every cancer possible. There are many environmental factors that could affect other types of cancer differently, like proximity to other organs. One major drawback of the Divoli et al. (5) study was that they did not use any scientific or experimental data—their entire study is based on the opinions of 28 humans. While these humans were experts in their fields, the sample size was extremely small compared to the different amounts of cancerous and metastatic situations that can arise. Ramis-Conde et al. (9) accounted for many factors that could inhibit the progression of cancerous cells through the body, but their study did not include any information on the timeframe of metastasis, where the metastases would occur, or the amount of metastasis locations that are possible. Liotta et al. (14) also neglected to identify any metastatic pathways or networks.

IV. Conclusion

Through this research, over ten different mathematical models of cancer were considered, including not just the Markov chains and partial differential equations mentioned here, but also ordinary differential equations (6), cellular automata (10), least squares and time-branching (4), and graph evolution (11), among others. The amount of data on the subject seems overwhelming, but it becomes clear why such a large number and different types of studies are necessary after learning more about the process and factors of metastasis. Since metastasis is such a multi-faceted, complex process with so many factors contributing to its progression, it would be extremely difficult to attempt to create one model to determine metastatic spread of all cancers and take into account every possible scenario. In the past few decades, researchers have developed studies on different aspects of the metastasis dilemma, such as how cancer leaves the primary tumor, how it travels through the body, factors in the body and cancer cells that prohibit it from surviving a journey, factors that allow cancer to settle in a new area, and what stages are included in the metastatic process. Since it is so problematic to establish a universal model, it is helpful to have models on so

many different stages of the disease that can be combined to determine an individual cancer's progression and decide the best course of treatment for that person. Ultimately, the largest benefit of these models is not to accurately predict the exact path the metastasis will take, but to be able to anticipate whether metastasis is likely or not. Once this is known, the physician can determine whether a general cancer treatment like chemotherapy is necessary or if removing the primary cancer with radiation or resection would be enough to rid the body of dangerous cancer cells. While the studies that were discussed have various limitations, there are results in each that can either be used or built upon to become beneficial instruments in the prognosis of cancer and increasing a patient's likelihood of remission.

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