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Solving inverse problems for biological models using the collage method for differential equations

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Abstract In the first part of this paper we show how inverse problems for differential equations can be solved using the so-called collage method. Inverse problems can be solved by minimizing the collage distance in an appropriate metric space. We then provide several numerical examples in mathematical biology. We consider applications of this approach to the following areas: population dynamics, mRNA and protein concentration, bacteria and amoeba cells interaction, tumor growth.

Keywords Collage Theorem · Inverse problems · Biological models

Mathematics Subject Classification (2000) 65L09 · 62P10

1 Inverse problems by the Collage Theorem

Many inverse problems or parameter identification problems may be viewed in terms of the approximation of a target element u in a complete metric space (X, d) by the fixed point $\bar{u}$ of a contraction mapping $T : X \to X$. Thanks to a simple consequence of Banach's fixed point theorem known as the *Collage Theorem*, most practical methods of solving the inverse problem for fixed point equations seek to find an operator T for which the *collage distance* $d(u, Tu)$ is as small as possible.

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Theorem 1 ("Collage Theorem" Barnsley 1989)
Let (X, d) be a complete metric space and $T : X \to X$ a contraction mapping with contraction factor $c \in [0, 1)$. Then for any $u \in X$,

$$d(u, \bar{u}) \leq \frac{1}{1-c} d(u, Tu), \tag{1}$$

where $\bar{u}$ is the fixed point of T.

One now seeks a contraction mapping T that minimizes the so-called *collage error* $d(u, Tu)$—in other words, a mapping that sends the target u as close as possible to itself. This is the essence of the method of *collage coding* which has been the basis of most, if not all, fractal image coding and compression methods. Barnsley (Barnsley et al. 1985; Barnsley 1989) was the first to see the potential of using the Collage Theorem above for the purpose of *fractal image approximation* which can be formulated as follows: Given a "target" self-similar set (or measure), say u, find a fractal transform operator T with fixed point $\bar{u}$ that is as close as possible to u.

From a practical perspective, however, it is difficult to construct solutions to this problem so one relies on the *Collage Theorem* and, instead of trying to minimize the error $d(u, \bar{u})$, one looks for a contraction mapping T that minimizes the so-called *collage error* $d(u, Tu)$. This is the essence of *fractal image coding* (Forte and Vrscay 1998). Other applications of the Collage Theorem can be found in Iacus and La Torre (2005a,b) and La Torre and Vrscay (2009). However, this method of *collage coding* may be applied in other situations where contractive mappings are encountered. We have shown this to be the case for inverse problems involving differential equations. In practical applications, from a family of contraction mappings $T_\lambda, \lambda \in \Lambda \subset \mathbb{R}^n$, one wishes to find the parameter $\bar{\lambda}$ for which the approximation error $d(u, \bar{u}_\lambda)$ is as small as possible, where $\bar{u}_\lambda$ is the fixed point of T_λ and c_λ is its contraction factor. In practical contexts the feasible set is defined to be $\Lambda = \{\lambda \in \mathbb{R}^n : 0 \leq c_\lambda \leq c < 1\}$ which guarantees the contractivity of T_λ for any $\lambda \in \Lambda$. This is the main difference between this approach and the one based on Tikhonov regularization (see Tychonoff and Arsenin 1997): in the collage approach, the constraint $\lambda \in \Lambda$ guarantees that T_λ is a contraction and, therefore, replaces the effect of the regularization term in the Tikhonov approach. In other words the collage-based inverse problem can be formulated as an optimization problem as follows:

$$\min_{\lambda \in \Lambda} d(u, T_\lambda u) \tag{2}$$

One possible technique to solve (2) is to use a penalty method which leads to the following unconstrained program

$$\min_{\lambda \in \mathbb{R}^n} d(u, T_\lambda u) + \sigma_1 \left[\max\{0, c_\lambda - 1\}\right]^2 + \sigma_2 \left[\max\{0, -c_\lambda\}\right]^2 \tag{3}$$

where σ_1 and σ_2 are two positive parameters. The meaning of this objective function is clear; when c_λ lies outside the interval $[0, 1)$, the objective function is augmented by positive quantities which affect the minimization process. Of course, this is a

nonsmooth optimization problem and the regularity of the objective function strictly depends on the term $d(u, T_\lambda u)$. As the next section shows, in many cases the first term can be reduced to a quadratic optimization problem. When this is not the case, alternative numerical algorithms can be used, as in Example III, where we used particle swarm ant colony optimization.

The paper is organized as follows. In Sect. 2 we briefly review the application of the collage method to deterministic and random ordinary differential equations. Several numerical applications of this approach to biological models are presented in Sect. 3. In particular, models in the following areas will be considered for the purpose of parameter identification: population dynamics, mRNA and protein concentration, bacteria and amoeba cells interaction, tumor growth.

2 Inverse problems for DEs by the Collage Theorem

In Kunze and Vrscay (1999) (and subsequent works Kunze and Gomes 2003; Kunze et al. 2004, 2007a,b, 2009a,b, 2010), the authors showed how collage coding could be used to solve inverse problems for systems of differential equations having the form

$$\begin{cases} \dot{u} = f(t, u), \\ u(0) = u_0, \end{cases} \tag{4}$$

by reducing the problem to the corresponding Picard integral operator associated with it,

$$(Tu)(t) = u_0 + \int_0^t f(s, u(s))\, ds. \tag{5}$$

Let us recall the basic results in the case when f belongs to L^2. Consider the complete metric space $C([0, \delta]; \mathbb{R}^n)$, $\delta > 0$, endowed with the usual d_∞ metric and assume that $f(t, x)$ is Lipschitz in the variable x i.e., there exists a $K \geq 0$ such that $\|f(s, x_1) - f(s, x_2)\| \leq K\|x_1 - x_2\|$, for all $x_1, x_2 \in \mathbb{R}^n$. Under these hypotheses T is Lipschitz on the space $C([0, \delta]; B_M(0))$ for some $M > 0$ where $B_M(0) = \{x \in \mathbb{R}^n : |x_i| \leq M\} \subseteq \mathbb{R}^n$.

Theorem 2 Kunze and Vrscay (1999) The function T satisfies

$$\|Tu - Tv\|_2 \leq c\|u - v\|_2 \tag{6}$$

for all $u, v \in C([0, \delta]; B_M(0))$ where $c = \delta K$.

We consider the inverse problem: given $u(t)$, $t \in [0, \delta]$, find a function f such that u is a solution of (4). In practical situations, only an approximation of u is available (in the form of experimental data) and an approximation of f can be recovered. This raises the problem that f may not be uniquely determined by (the data) u. Typically,

in order to solve the inverse problem an L^2 expansion of the function f is taken and the collage distance is then understood in the L_2 sense.

Now let $\delta' > 0$ be such that $\delta' K < 1$. Let $\{\phi_i\}$ be a basis of functions in $L^2([-\delta', \delta'] \times B_M(0))$ and consider

$$f_\lambda(s, x) = \sum_{i=1}^{+\infty} \lambda_i \phi_i(s, x). \tag{7}$$

Each sequence of coefficients $\lambda = \{\lambda_i\}_{i=1}^{+\infty}$ then defines a Picard operator T_λ. Suppose further that each function $\phi_i(s, x)$ is Lipschitz in x with constants K_i.

Theorem 3 Kunze and Vrscay (1999) Let $K, \lambda \in \ell^2(\mathbb{R})$. Then

$$|f_\lambda(s, x_1) - f_\lambda(s, x_2)| \leq \|K\|_2 \|\lambda\|_2 |x_1 - x_2| \tag{8}$$

for all $s \in [-\delta', \delta']$ and $x_1, x_2 \in B_M(0)$ where $\|K\|_2 = \left(\sum_{i=1}^{+\infty} K_i^2\right)^{\frac{1}{2}}$ and $\|\lambda\|_2 = \left(\sum_{i=1}^{+\infty} \lambda_i^2\right)^{\frac{1}{2}}$

In this setting, the Collage Theorem (1) says

$$\|u - \bar{u}_\lambda\|_2 \leq \frac{1}{1 - c_\lambda} \|u - T_\lambda u\|_2.$$

Given a target solution u, to control the true error in approximating u by $\bar{u}_\lambda$, we seek to minimize the collage distance $\| u - T_\lambda u \|_2$. The square of the collage distance becomes

$$\begin{aligned} \Delta^2(\lambda) &= \|u - T_\lambda u\|_2^2 \\ &= \int_0^\delta \left| u(t) - u_0 - \int_0^t \sum_{i=1}^{+\infty} \lambda_i \phi_i(s, u(s)) ds \right|^2 dt \end{aligned} \tag{9}$$

and the inverse problem can be formulated as

$$\min_{\lambda \in \Lambda} \Delta(\lambda), \tag{10}$$

where $\Lambda = \{\lambda \in \ell^2(\mathbb{R}) : \|\lambda\|_2 \|K\|_2 < 1\}$. To solve numerically this problem, let us consider the first n terms of the L^2 basis; in this case the previous problem can be reduced to:

$$\min_{\lambda \in \tilde{\Lambda}} \tilde{\Delta}^2(\lambda) = \int_0^\delta \left| u(t) - \int_0^t \sum_{i=1}^{n} \lambda_i \phi_i(s, u(s)) ds \right|^2 dt, \tag{11}$$

where $\tilde{\Lambda} = \{\lambda \in \mathbb{R}^n : \|\lambda\|_2 \|K\|_2 < 1\}$. This is a classical quadratic optimization problem which can be solved by means of classical numerical methods. A penalized version of (11) is the following

$$\min_{\lambda \in \mathbb{R}^n} \tilde{\Delta}^2(\lambda) + \sigma_1 \max\{0, \|\lambda\|_2^2 \|K\|_2^2 - 1\}^2, \tag{12}$$

where $\sigma_1 > 0$ is a parameter. Let $\tilde{\Delta}^n_{\min}$ be the minimum value of $\tilde{\Delta}$ over $\tilde{\Lambda}$. This is a non increasing sequence of numbers (depending on n). Using the same method of proof as in Forte and Vrscay (1998), it is possible to show that $\liminf_{n \to +\infty} \tilde{\Delta}^n_{\min} = 0$. This states that the distance between the target element and the unknown solution of the differential equation can be made arbitrary small.

In Kunze et al. (2007b), Kunze, La Torre and Vrscay considered the case of inverse problems for random differential equations. This kind of formulation allows one to include, in a unique theoretical approach, the effects of noise/random perturbations on the solutions of differential equations. It can be formulated as

$$\begin{cases} \frac{d}{dt} u(\omega, t) = f(t, \omega, u(\omega, t)), \\ u(\omega, 0) = u_0(\omega). \end{cases} \tag{13}$$

where both the vector field f and the initial condition u_0 are random variables defined on an appropriate probability space $(\Omega, \mathscr{F}, P)$. Analogous to the deterministic case, for $X = C([0, T])$ this problem can be reformulated by using the following random integral operator $T : \Omega \times X \to X$:

$$(T(\omega, u))(t) = u_0(\omega) + \int_0^t f(s, \omega, u(s))\, ds. \tag{14}$$

Solutions to (13) are fixed points of (14), that is, solutions of the equation $T_\omega u = u$. We recall that a function $T : \Omega \times X \to X$ is called a *random operator* if for any $u \in X$ the function $T(\cdot, u)$ is measurable. The random operator T is said to be continuous/Lipschitz/contractive if, for a.e. $\omega \in \Omega$, we have that $T(\omega, \cdot)$ is continuous/Lipschitz/contractive. A measurable mapping $u : \Omega \to X$ is called a *random fixed point* of the random operator T if u is a solution of the equation

$$T(\omega, u(\omega)) = u(\omega), \quad a.e.\ \omega \in \Omega. \tag{15}$$

In order to study the existence of solutions to such equations, let us consider the space Y of all measurable functions $u : \Omega \to X$. If we define the operator $\tilde{T} : Y \to Y$ as $(\tilde{T}u)(\omega) = T(\omega, u(\omega))$ the solutions of this fixed point equation on Y are the solutions of the random fixed point equation $T(\omega, u(\omega)) = u(\omega)$. The space Y is a complete metric space with respect to the following metric (see Kunze et al. 2007b):

$$d_Y(u_1, u_2) = \int_\Omega d_X(u_1(\omega), u_2(\omega)) dP(\omega). \tag{16}$$

Table 1 Minimal collage distance parameters for different N and M, to five decimal places

N	M	b	a
100	300	3.78599	1.69618
100	600	4.33750	1.78605
100	1,000	4.05374	1.85780
300	300	3.34231	1.80282
300	600	3.54219	1.81531
300	1,000	3.84973	1.78323

As the following Example 1 shows, it is possible to use the collage error-based approach for solving inverse problems for certain classes of stochastic processes.

Example 1 Suppose that the stochastic process X_t is believed to follow a geometric Brownian motion; then it satisfies the stochastic differential equation

$$dX_t = aX_t\,dt + bX_t\,dW_t, \tag{17}$$

subject to the initial deterministic condition $X_0 = x_0$, where W_t is a Wiener process and the constants a and b are the percentage drift and the percentage volatility, respectively. We consider the inverse problem: given realizations/paths X_t^i, $1 \le i \le N$, estimate the values a and b. Taking the integral form of (17) and then the expectation of both sides, we see that $\mathbb{E}(X_t)$ satisfies the simple fixed point equation

$$\mathbb{E}(X_t) = T(\mathbb{E}(X_t)) = x_0 + \int_0^t a\mathbb{E}(X_r)\,dr. \tag{18}$$

Hence, to solve the inverse problem, we construct the mean of the realizations

$$X_t^* = \frac{1}{N}\sum_{i=1}^{N} X_t^i \tag{19}$$

and use collage coding to determine the value of a that minimizes the collage distance $d\left(X_t^*, TX_t^*\right)$. We can then estimate the value of b by using the known formula $var(X_t) = e^{2at}x_0^2\left(e^{b^2t} - 1\right)$, approximating $var(X_t)$ from the realizations. As an example, we set $a = 2, b = 4$, and $x_0 = 1$, and then generate N paths on $[0, 1]$, dividing the interval into M subintervals in order to simulate the Brownian motion on $[0, 1]$. Beginning with these paths, we seek estimates of a and b using collage coding. Table 1 presents the numerical results of the example.

Before ending this section, it is worthwhile to discuss the possibility of using the collage error-based approach for infinite dimensional spaces, for instance when analyzing differential equations in Banach spaces. In fact it is known that several results

which are true in finite dimensional spaces are no longer true when infinite dimensional spaces are considered (this is the case, for instance, of Peano's theorem). A result which guarantees the existence and uniqueness of a solution of a Cauchy problem in Banach space is the Osgood theorem (see Shkarin 2003 for more details). Under the hypotheses of this result, an inverse problem for a Cauchy problem in a Banach space can be stated in the usual manner. However, from a computational point of view, it is essential to require that the Banach space X admits a Schauder basis[1]. One classical example of Schauder basis is the Haar system in $L^p(0, 1)$ with $1 \leq p < \infty$. Using the elements of a Schauder basis it is possible to proceed by finite approximations.

3 Applications to biological models

Many models in biology can be formulated in terms of deterministic and random differential equations (see Capasso 2008). In this section we present how to solve inverse problems for some dynamical models by using the collage method described above.

3.1 Example I

Population dynamics has played a crucial role in both mathematical biology and economic growth modelling. Its long history started with the exponential law of Malthus and the Malthusian growth model. Many contributions in the literature (see, for instance, Bucci and La Torre 2009; La Torre and Marsiglio 2010 and the references therein) have highlighted the impact of population size on economic growth, the production function GDP, labor supply and savings, and so on. According to up-to-date demographic forecasts (United Nations webpage, http://www.un.org), the world population annual growth rate is expected to fall gradually from 1.8% (1950–2000) to 0.9% (2000–2050), before reaching a value of 0.2% between the years 2050 and 2100.

Following Lotka (1925), population dynamics can be described through a non-autonomous differential equation as $\dot{L}(t) = L(t)g(L(t))$ (if $L(t) = 0$ then there is no population growth). We are interested in the estimation of the function g through the solution of a parameter identification problem. In many papers in the literature g is supposed to be constant (which leads to an exponential population growth) or to be equal to $n - dL(t)$ (which implies a logistic behavior), with $n, d > 0$. This data-driven identification problem allows us to determine which is the suitable model to describe the population dynamics, providing a way to forecast the long-run demographic behavior. Here we wish to solve an inverse problem for this kind of differential equation, using the above collage method and real data available at the Angus Maddison webpage (http://www.ggdc.net/MADDISON/oriindex.htm).

We use data in six continents (Africa, Asia, Australia, Europe, South America, and North America) over the period 1870–2008 and we look for a polynomial solution of

[1] A Schauder basis is a sequence ϕ_n of elements of X such that for every element $x \in X$ there exists a unique sequence α_n of elements in $\mathbb{R}$ so that $x = \sum_n \phi_n x_n$ where the convergence is understood with respect to the norm topology.

Table 2 Minimal collage distance parameters

	g_0	g_1	g_2	g_3
Africa	−0.00763537	0.00000018	−0.00000000	0.00000000
Asia	−0.02926752	0.00000005	−0.00000000	0.00000000
Australia	0.03003342	−0.00000383	0.00000000	−0.00000000
Europe	0.12968633	−0.00000070	0.00000000	−0.00000000
South America	0.00203530	0.00000025	−0.00000000	0.00000000
North America	0.03432962	−0.00000030	0.00000000	−0.00000000

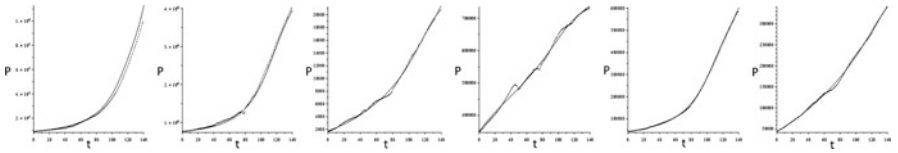

Fig. 1 Population dynamics in Africa, Asia, Australia, Europe, South America, and North America. The origin corresponds to the year 1870

the form

$$g(u) = \sum_{i=0}^{m} g_i u^i, \tag{20}$$

where the g_i constant coefficients. This leads to

$$\dot{L}(t) = \sum_{i=1}^{m+1} g_i L^i(t) \tag{21}$$

The results to eight decimal digits (using third-order polynomials) are provided in Table 2. The solution of the inverse problem suggests that a good fitting curve for Australia, Europe, and North America for this data is the logistic one (see Fig. 1) while South America shows an exponential behavior ($g_0, g_1 > 0$). Africa and Asia show a negative coefficient g_0 which can be justified in terms of migration effects.

3.2 Example II

In Smiley and Proulx (2010), a simple stochastic model of gene regulation is presented. The authors consider a two-stage model of mRNA $x(t)$ and protein concentration $y(t)$ described by the following system of ODEs

$$\frac{dx}{dt} + \mu_r x = R(t) \tag{22}$$

$$\frac{dy}{dt} + \mu_p y = r_p x, \tag{23}$$

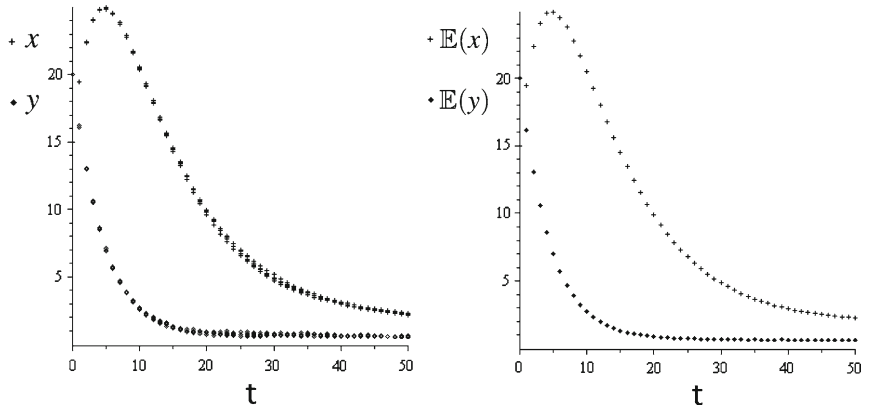

Fig. 2 Realizations (*left*) and mean values (*right*) for the mRNA (*cross*) and protein (*diamond*) system

where μ_r and μ_p are the decay rates of mRNA and protein, respectively, r_p is the environment independent rate at which protein is translated from active mRNA, and $R(t)$ is the continuous-time two-state Markov process modeling the switching environmental conditions. That is, $R(t)$ is assumed to switch between two states r_0 and r_1. The two-state model corresponds to a system where the gene's enhancer sites can be bound to by different transcription factors or cofactors. Once bound, transcription occurs at a constant rate, and the mRNA product breaks down at a constant rate μ_r. On the other hand, the protein production depends upon the concentration of mRNA. The model gives rise to a join stochastic process for the levels of mRNA and protein.

Given observations of numerous realizations of the stochastic variables, the goal of the inverse problem is to recover the two decay rates and the mRNA-to-protein translation rate. As the below system (24) shows—thanks to linearity—this can be done by taking the expectations of both sides and then by estimating the expected values by using a finite set of observations.

The expected values of x and y satisfy the system

$$\frac{d\mathbb{E}(x)}{dt} + \mu_r \mathbb{E}(x) = p_0 r_0 + (1 - p_0) r_1 \tag{24}$$

$$\frac{d\mathbb{E}(y)}{dt} + \mu_p \mathbb{E}(y) = r_p \mathbb{E}(x). \tag{25}$$

As an experiment, we set $\mu_r = 0.2$, $\mu_p = 0.1$, and $r_p = 0.3$. Furthermore, we set $r_0 = 0.2$, $r_1 = 0.1$, and define the Markov process to select state r_0 with probability 0.25. For each of 100 realizations, we generate 50 data values, one time unit apart. The values of five realizations as well as the mean values of the 100 realizations are plotted in Fig. 2. Hence we seek the parameters α_1, α_2, β_1, and β_2 of the system

$$\frac{dx}{dt} + \alpha_1 x = \alpha_2 \tag{26}$$

$$\frac{dy}{dt} + \beta_1 y = \beta_2 x \tag{27}$$

that minimize the corresponding squared L_2 collage distances

$$\Delta_x^2 = \int_0^{50} \left(x(t) - \int_0^t (\alpha_2 - \alpha_1 x(s))\, ds \right)^2 dt \tag{28}$$

$$\Delta_y^2 = \int_0^{50} \left(y(t) - \int_0^t (\beta_2 x(s) - \beta_1 y(s))\, ds \right)^2 dt. \tag{29}$$

Note that the actual value of $\alpha_2 = p_0 r_0 + (1 - p_0) r_1 = 0.125$. As shown in the first and second paragraph, we solve a penalized version of this model which provides the following results

$$\alpha_1 = 0.200, \quad \alpha_2 = 0.127, \quad \beta_1 = 0.100, \quad \beta_2 = 0.300. \tag{30}$$

Increasing the number of realizations moves us even closer to this value.

3.3 Example III

In Fumanelli et al. (2011), the authors present the following model, which describes the dynamics for the pathogenesis mechanism of the opportunistic human pathogen *Pseudomonas aeruginosa* in co-culture with *Dictyostelium* amoebae:

$$\frac{du}{dt} = r\left(1 - \frac{u}{K}\right) u - auv \tag{31}$$

$$\frac{dv}{dt} = -mv + duv - \frac{buv}{1 + bTv}, \tag{32}$$

where $u(t)$ and $v(t)$ are the number of bacteria and amoeba cells, respectively, at time t. In the absence of the amoeba, the bacteria undergo logistic growth with intrinsic growth rate r and carrying capacity K. In the absence of bacteria, the amoeboid population undergoes an exponential growth decay with death rate m, as the bacteria are assumed to be the unique food source for the amoeba. The amoeba cells feed on bacteria through a mass-action mechanism with attack rate a. The amoeba growth rate is proportional to the uptake of bacteria, with proportionality constant d. Finally, bacteria attack and kill amoeba cells according to a Holling-type function with handling time T and attack rate b.

We consider the inverse problem of recovering all of the constant rates in the model equations from observations of the bacteria and amoeba populations.

For a simulation, we set $r = 0.6$, $K = 10$, $a = 0.6$, $m = 0.52$, $d = 0.6$, $b = 0.44$, and $T = 3.25$. The system admits the stable equilibrium point (1.286, 0.871), to three decimal places. The solution trajectories with $u(0) = 8$ and $v(0) = 6$ are illustrated in Fig. 3.

We simulate the gathering of observational data $u_i = u(t_i), v_i = v(t_i)$ times $t_i = 0.1i, 0 \leq i \leq 400$, in order to capture the behaviour of the two "spikes".

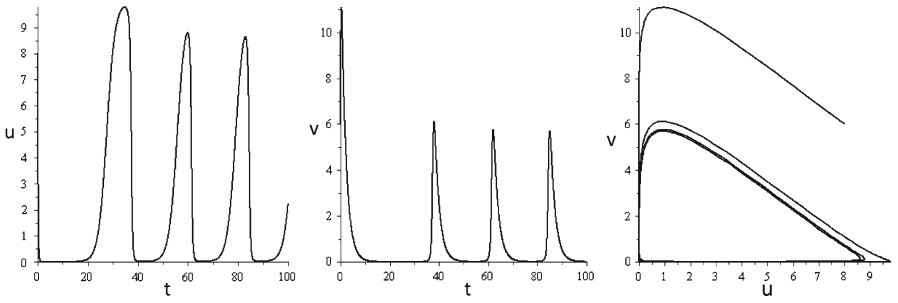

Fig. 3 Plots of the number of bacteria u and the number of amoeba cells v for our simulation

Given these two sets of data, we seek to recover the parameters α_j, $j = 1, 2, 3$, and β_j, $j = 1, 2, 3, 4$, so that the system

$$\frac{du}{dt} = \alpha_1 (1 + \alpha_2 u)\, u + \alpha_3 uv \tag{33}$$

$$\frac{dv}{dt} = \beta_1 v + \beta_2 uv + \frac{\beta_3 uv}{1 + \beta_3 \beta_4 v}. \tag{34}$$

admits the data sets as an approximate solution. The associated squared L^2 collage distances are

$$\Delta_u^2 = \int_0^{40} \left(u(t) - u(0) - \int_0^t (\alpha_1 (1 + \alpha_2 u(s))\, u(s) + \alpha_3 u(s) v(s))\, ds \right)^2 dt \tag{35}$$

$$\Delta_v^2 = \int_0^{40} \left(v(t) - v(0) - \int_0^t \left(\beta_1 v(s) + \beta_2 u(s) v(s) + \frac{\beta_3 u(s) v(s)}{1 + \beta_3 \beta_4 v(s)} \right) ds \right)^2 dt. \tag{36}$$

A penalization method allows to include the constraints into the objective function; we discretize the problem in accordance with the observational data interval and seek to find the parameters that minimize the objective function. For Δ_u^2, the method yields, to four decimal places, $\alpha_1 = 0.6012$, $\alpha_2 = -0.0603$, and $\alpha_3 = -0.5940$. The squared collage distance Δ_v^2 is a more complicated function of its parameters, so we use particle swarm ant colony optimization to minimize it (see Ostfeld 2011). We obtain $\beta_1 = -0.5182$, $\beta_2 = 0.5795$, $\beta_3 = -0.5131$, and $\beta_4 = 2.5274$. The values for the α_i, β_1, and β_2 agree well with the known values. The values for β_3 and β_4 are further away from the expected values of -0.44 and 1.43.

3.4 Example IV

We consider a shape analysis inverse problem that models the evolution of a tumor. At each time t, we suppose that a tumor occupies the region $u(t)$. The level of a

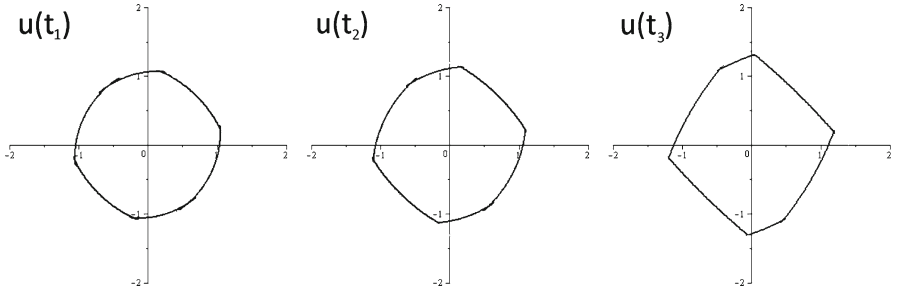

Fig. 4 Snapshots in the evolution of our simulated tumor

diffusing nutrient concentration determines whether the tumor grows or shrinks due to cell proliferation or death. In Friedman and Reitich (1999), under the assumption that the tumor is always spherical, the problem is cast as a free-boundary problem in three spatial dimensions. Here, we assume that the tumor always occupies a convex region that encloses the origin, and we work in two spatial dimensions for convenience: the ideas extend to three dimensions. Given observational data, we wish to recover a model in the differential form

$$u(t + dt) = u(t) + [(Au)(t) + b]dt \tag{37}$$

where for each fixed t, we have $u(t) \in \mathbb{H}_c$ is a compact and convex subset of $\mathbb{R}^2$ and the sum is understood in the Minkowski sense. The convexity assumption means that we can codify this model in terms of an infinite dimensional operator A and an infinite-dimensional vector b that capture the growth rate information in every direction. The real-world problem is: given observational data in $N < \infty$ directions, recover an N-dimensional model

$$\frac{du_N}{dt} = A_N u_N + b_N \tag{38}$$

that approximates well the evolution of the tumor. As an example, we construct an always-convex region by considering the intersection of several rotated, time-varying ellipses. Three of the frames in the region's evolution are given in Fig. 4. To simulate the data gathering process, we calculate the position of the frontier of the tumor along N uniformly-distributed rays through the origin. This corresponds to an N-dimensional model of Eq. (38), with dimension i corresponding to the growth along ray i. In Fig. 5, we present visual results for the case $N = 40$; for the same three times illustrated in Fig. 4, we plot the data points produced by the model we have recovered, connecting them with straight line segments. Denoting by $A(t)$ the area of the tumor at time t, we can use the model to calculate and forecast the relative growth rate of the area of the tumor, $\frac{A'(t)}{A(t)}$. In Table 3, we present some results for different values of N. In this case, the models show that the relative growth rate of the tumor is decreasing.

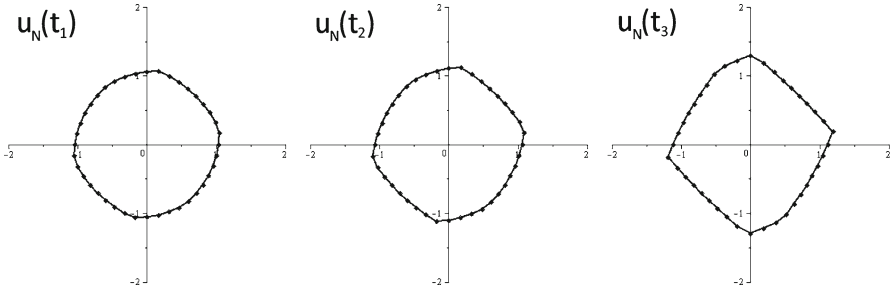

Fig. 5 Snapshots produced by our recovered model with $N = 40$

Table 3 Model calculations for the relative growth rate $\frac{A'(t)}{A(t)}$ of the tumor.

time t	$N = 20$	$N = 40$	$N = 60$
0.2	0.0434	0.0453	0.0458
0.4	0.0411	0.0430	0.0434
0.6	0.0390	0.0408	0.0411
0.8	0.0370	0.0387	0.0390
1.0	0.0352	0.0368	0.0352
2.0	0.0291	0.0304	0.0304
3.0	0.0236	0.0244	0.0243
4.0	0.0196	0.0201	0.0198
5.0	0.0168	0.0170	0.0166

4 Conclusions

In this paper we proposed a Collage Theorem-based approach for solving inverse problems for differential equations. The method was illustrated through several examples in different biological contexts; they showed the goodness of this approach as well as its stability with respect to data perturbations.

References

Barnsley MF, Ervin V, Hardin D, Lancaster J (1985) Solution of an inverse problem for fractals and other sets. Proc Natl Acad Sci 83:1975–1977

Barnsley MF (1989) Fractals everywhere. Academic Press, New York

Bucci A, La Torre D (2009) Population and economic growth with human and physical capital investments. Int Rev Econ 56(1):17–27

Capasso V (2008) Mathematical structures of epidemic systems, 2nd edn. Springer, Berlin

Forte B, Vrscay ER (1998) Inverse problem methods for generalized fractal transforms. In: Fisher Y (ed) Fractal image encoding and analysis. NATO ASI Series F, 159, Springer, New York

Friedman A, Reitich F (1999) Analysis of a mathematical model for the growth of tumors. J Math Biol 38:262–284

Fumanelli L, Iannelli M, Janjua HA, Jousson O (2011) Mathematical modeling of bacterial virulence and host–pathogen interactions in the *Dictyostelium*/*Pseudomonas* system. J Theor Biol 270:19–24

Iacus SM, La Torre D (2005) A comparative simulation study on the IFS distribution function estimator. Nonlinear Anal Real World Appl 6(5):858–873

Iacus SM, La Torre D (2005) Approximating distribution functions by iterated function systems. J Appl Math Decis Sci 1:33–46
Kunze H, Gomes S (2003) Solving an inverse problem for Urison-type integral equations using Banach's fixed point theorem. Inverse Probl 19:411–418
Kunze H, Hicken J, Vrscay ER (2004) Inverse problems for ODEs using contraction functions: suboptimality of the "Collage Method". Inverse Probl 20:977–991
Kunze H, Vrscay ER (1999) Solving inverse problems for ordinary differential equations using the Picard contraction mapping. Inverse Prob 15:745–770
Kunze H, La Torre D, Vrscay ER (2007) Contractive multifunctions, fixed point inclusions and iterated multifunction systems. J Math Anal Appl 330:159–173
Kunze H, La Torre D, Vrscay ER (2007) Random fixed point equations and inverse problems using collage method for contraction mappings. J Math Anal Appl 334:1116–1129
Kunze H, La Torre D, Vrscay ER (2009) Inverse problems for random differential equations using the collage method for random contraction mappings. J Comput Appl Math 223(2):853–861
Kunze H, La Torre D, Vrscay ER (2009) A generalized collage method based upon the Lax-Milgram functional for solving boundary value inverse problems. Nonlinear Anal Theory Methods Appl 71(12):e1337–e1343
Kunze H, La Torre D, Vrscay ER (2010) Solving inverse problems for variational equations using the "generalized collage methods," with applications to boundary value problems. Nonlinear Anal Real World Appl 11(5):3734–3743
La Torre D, Marsiglio S (2010) Endogenous technological progress in a multi-sector growth model. Econ Model 27(5):1017–1028
La Torre D, Vrscay ER (2009) A generalized fractal transform for measure-valued images. Nonlinear Anal 71(12):e1598–e1607
Lotka AJ (1925) Elements of physical biology. Williams and Wilkins, Baltimore
Ostfeld A (2011) Ant colony optimization—methods and applications. InTech
Shkarin S (2003) On Osgood theorem in Banach spaces. Mathematische Nachrichten 257:87–98
Smiley MW, Proulx SR (2010) Gene expression dynamics in randomly varying environments. J Math Biol 61:231–251
Tychonoff AN, Arsenin VY (1997) Solution of ill-posed problems. Winston, Washington