CLINICAL CARDIOVASCULAR IDENTIFICATION WITH LIMITED DATA AND FAST FORWARD SIMULATION

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Abstract: A minimal cardiac model has been developed that captures the major dynamics of the cardio-vascular system (CVS). This model is extended to simulate time varying disease state including reflex actions and an integral based identification method is presented that enables linear and convex parameter identification. Two common time varying disease states are identified to within 10% without false identification. Also the valve law in this model is reformulated in terms of Heaviside functions, and a unique closed form analytical solution is obtained for the ventricular interaction equation. This enables rapid forward simulations of the model. Clinically, the method ensures medical staff can rapidly obtain a patient specific model and can simulate a large number of therapy combinations to find the best treatment. *Copyright © 2006 IFAC*

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1. INTRODUCTION

Cardiovascular disease is difficult to diagnose and treat due to limited measurements available in an Intensive Care Unit (ICU). The particular disease state does not generally show up with any individual measurement but involves complex interactions between a wide range of data including the body's natural reflex response which seeks to restore circulatory equilibrium. Thus often diagnosis and the chosen treatment depends on the experience and intuition of clinical staff.

A minimal cardiac model which captures all the major dynamics and interactions observed in stan-dard clinical measurements and can be tailored to an individual patient, could therefore assist medical staff in diagnosis and the prediction of drug effects to optimize therapy. "Minimal" model refers to a model that minimizes the number of parameters while still capturing the essential macro dynamics of the CVS within the measurements available.

There is a variety of CVS models in the literature that range from very complex finite element models to more relatively simpler pressure volume approaches. Although there are models that describe the whole CVS, patient specific parameter optimization is either not considered or

restricted to small subsets of the whole parameter set describing specific aspects of the CVS (e.g. (Mukkamala and Cohen, 2001)). The approach of this research is to develop a highly flexible minimal model that can adapt to wide ranges of patient dynamics seen in an ICU, including responses to potentially many different therapies. In the ICU environment, catheters are often already in place so a larger range of measurements are available. Furthermore, as this paper shows, using an integral based optimization enables virtually all of the parameter set to be identified.

This research builds on a previously developed minimal model which accurately simulates a variety of CVS dysfunctions, (Smith *et al.*, 2004). However, the model does not lend itself to a convex identification problem (Smith, 2004). Thus, potentially false solutions could be found. Furthermore, to implement common non-linear regression identification methods (Carson and Cobelli, 2001) requires many computationally expensive model simulations (Smith, 2004). Hence, computational intensity severely limits the number of optimization iterations available to find a solution in a clinically useful time period.

In this paper, an integral-based patient specific identification method is presented which is an extension of (Hann *et al.*, 2005; Hann *et al.*, 2004). All measurements assumed are available in critical care using Swan-Ganz catheters or ultra-sound.

Two common disease states, Pericardial Tamponade and Cardiogenic shock are simulated from onset. Each disease state is then identified in the presence of 10% uniformly distributed noise to prove the concept. The body's reflex actions to keep the pressure in the aorta stable are included.

Also a fast forward solver is critical as there remains the task of trialling many different therapies to find the best treatment. Two methods of significantly speeding up the current model are discussed.

2. METHODOLOGY

2.1 Cardiac Model

The full model consists of six elastic chambers as shown in Figure 1. Each of the ventricles is treated as a single elastic chamber. The differential equations for the single elastic chamber with inertia and upstream and downstream pressures P_1 and P_3, are defined (Smith *et al.*, 2004):

$$\dot{V} = Q_1 - Q_2 \tag{1}$$

$$\dot{Q}_1 = \frac{P_1 - P_2 - Q_1 R_1}{L_1} \tag{2}$$

$$\dot{Q}_2 = \frac{P_2 - P_3 - Q_2 R_2}{L_2} \tag{3}$$

where Q_1 and Q_2 are the flows in and out, L_1 and L_2 are inertances of the blood, R_1 and R_2 are resistances. The driving pressure in the chamber is defined:

$$P_2 = e(t)E_{es}(V - V_d)$$
$$+ (1 - e(t))P_0(e^{\lambda(V - V_0)} - 1) \tag{4}$$

$$e(t) = e^{-80(t - 0.375)^2} \tag{5}$$

where E_{es} is elastance, V_d is the unstressed chamber volume, $e(t)$ is a driving function that simulates ventricular contraction and P_0, λ, and V_0 define gradient, curvature and volume at zero pressure of the EDPVR curve in the cardiac cycle shown in Figure 2 (Smith *et al.*, 2004).
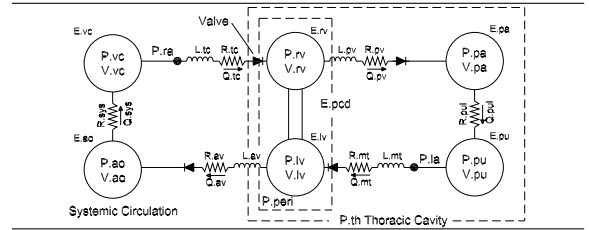

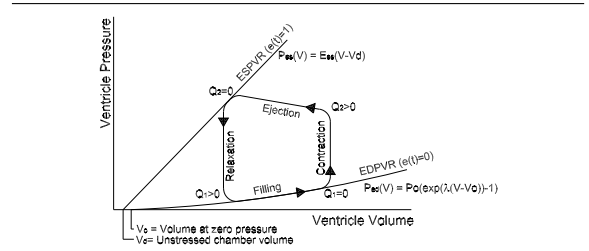Fig. 1. The full six chamber cardio-vascular system model

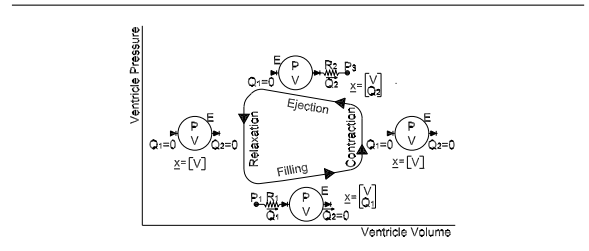Fig. 2. Pressure-volume diagram of the single cardiac chamber model.

Fig. 3. Model state at each part of the cardiac cycle.

The original solution procedure (Smith *et al.*, 2004) for incorporating valve dynamics in the chambers is to solve the Equations (1) and (2) when $Q_1 > 0$, during the filling stage, and to solve Equations (1) and (3) when $Q_2 > 0$, during the ejection stage. This model has an open on pressure, close on flow valve law as shown in Figure 2 (Smith *et al.*, 2004; Smith, 2004). Figure 3 shows the states used for each portion of the cardiac cycle.

2.2 Reflex actions

The effect of heart disease and shock on the CVS can be significantly altered by the body's natural reflex response that attempts to maintain enough blood pressure and flow to sustain life. The effect of reflex actions can thus often mask the underlying problem and must be accounted for in the CVS model.

Reflex actions included are divided into four groups: vaso-constriction, venous constriction, increased heart rate (HR) and increased ventricular contractility (Burkhoff and Tyberg, 1993). Their activation is assumed to be proportional to the drop in the average pressure in the aorta (P_{ao}). The proportionality constants are estimated based on clinically observed CVS hemodynamic responses reported in the literature (Braunwald, 1997).

Specifically, vaso-constriction is simulated in the model based on increasing the systemic resistance R_{sys} by 35% for a drop in average P_{ao} from 100 mmHg to 80 mmHg. Similarly, venous constriction, HR and ventricular contractility are increased based on increasing the venous dead space $V_{d,vc}$, HR and the left and right ventricle free wall contractilities $E_{es,lvf}$ and $E_{es,rvf}$ by 67%, 80 to 120 beats per minute and 35% respectively for a drop in average P_{ao} to 80 mmHg. In the model simulations, reflex actions are applied every heart beat.

2.3 Integral parameter identification

The differential equations associated with the left and right ventricles can be reformulated in terms of integrals of the measured flows through the chambers, see (Hann et al., 2004). Similarly the differential equations of (Smith et al., 2004) describing volume changes in the aorta, pulmonary artery, vena cava and pulmonary vein can be reformulated in terms of integrals by choosing suitable sampling periods.

The end result is that given the pressure waveforms through the aorta and pulmonary artery, the flows into and out of the left and right ventricles and their maximum and minimum volumes, a system of linear equations can be defined:

$$A\underline{\beta} = b \qquad (6)$$
$$\underline{\beta} = [\underline{\alpha}, P_{ao0}, P_{pu0}, P_{pa0}, P_{vc0}] \qquad (7)$$

$$\underline{\alpha} = [L_{av}, L_{mt}, L_{tc}, L_{pv}, E_{es,lvf}, P_{0,lvf}, E_{es,rvf},$$
$$P_{0,rvf}, R_{av}, R_{mt}, R_{tc}, R_{pv}, E_{vc}, E_{pu}, E_{ao}, E_{pa},$$
$$R_{sys}, R_{pul}] \qquad (8)$$

where A is an $N \times 22$ matrix, $N >> 22$ is the number of chosen integration periods over which the parameters are constant, b is an $N \times 1$ vector, $\underline{\alpha}$

are the patient specific parameters and the initial conditions, P_{ao0}, P_{pu0}, P_{pa0} and P_{vc0} are treated as extra unknown variables. Equation (6) can then be solved by linear least squares to uniquely determine $\underline{\alpha}$.

2.4 Simulating Disease States

The disease states that are simulated are Pericardial Tamponade and Cardiogenic Shock. Pericardial tamponade is an excessive build up of fluid in the pericardium limiting ventricular expansion. It is simulated by reducing the pericardium deadspace volume $V_{0,pcd}$ by 20 ml every 10 heart beats for a total of 50 heart beats.

Cardiogenic shock occurs when the heart is unable to pump a sufficient amount of blood to provide oxygen to the tissues and myocardium (Braunwald, 1997). Lack of oxygen supply to the myocardium causes further depression of cardiac function by decreasing ventricular contractilities and increasing diastolic elastance. Hence, a patient beginning to suffer from left ventricular infarction due to a coronary artery becoming blocked is simulated from an initial healthy state. The left ventricle contractility is reduced in piecewise constant steps to 50% of normal and diastolic elastance is increased in piecewise constant steps to a factor of 2.5 due to ischemia.

2.5 Heaviside formulation and Ventricular Interaction

For the full model described in (Smith et al., 2004) there are two valves for each of the left and right ventricles giving rise to a number of combinations of open and closed positions of the valves to capture. This formulation can be coded with some effort, but is computationally heavy, constantly searching for sign changes in model states. Another significantly simpler formulation that does not require an event solver is to automatically account for the valve opening or closing using Heaviside functions.

For the left ventricle the upstream pressure P_1 is the pressure in the pulmonary vein (P_{pu}) and the downstream pressure P_2 is the pressure in the aorta (P_{ao}). The Heaviside formulation of Equations (1)-(3) is defined as follows:

$$\dot{V} = H(Q_1)Q_1 - H(Q_2)Q_2 \qquad (9)$$
$$\dot{Q}_1 = H\left(H(P_1 - P_2) + H(Q_1) - 0.5\right)$$
$$\frac{(P_1 - P_2 - R_1Q_1)}{L_1}$$
$$\qquad (10)$$
$$\dot{Q}_2 = H(H(P_2 - P_3) + H(Q_2) - 0.5)$$
$$\frac{(P_2 - P_3 - R_2Q_2)}{L_2}$$
$$\qquad (11)$$

where the Heaviside function $H(K(t))$ is defined:

$$H(K(t)) = 0, \quad K(t) < 0$$
$$= 1, \quad K(t) \geq 0 \qquad (12)$$

Note that a more compact form for the Heaviside function can be defined as follows:

$$H(K(t)) = \frac{1}{2} + \frac{1}{\pi}\left(\tan^{-1}(K(t)) + \tan^{-1}(\frac{1}{K(t)})\right) \qquad (13)$$

By using a triangle with base $K(t)$ and height 1 it is easily shown that Equation (13) and (12) are precisely equivalent. Simulations have shown that Equation (13) is a computationally more efficient form than Equation (12).

During filling, $Q_2 = 0$ and $P_2 < P_3$ so the right hand side of Equation (11) is zero and thus Q_2 remains at zero and Equations (9)-(10) are solved. The pressure P_2 will then increase but when P_2 becomes greater than P_1, the inlet valve does not shut off (that is $\dot{Q}_1 = 0$) until Q_1 becomes 0 or negative. This implementation of the close on flow portion of the valve law occurs because

$$H(H(P_1 - P_2) + H(Q_1) - 0.5) = 1,$$
$$P_2 > P_1, \ Q_1 > 0$$
$$H(H(P_1 - P_2) + H(Q_1) - 0.5) = 0,$$
$$P_2 > P_1, \ Q_1 \leq 0$$

Hence, this valve law captures the effect of inertia for the inlet valve by closing on flow.

The explanation for the contraction, ejection and relaxation periods is similar. This cycle is continued for as many heart beats as required. Thus, the two flow differential equations and the volume differential equation are solved simultaneously for all time without needing the event solver to switch models and sets of equations (Smith, 2004). All that is required are initial conditions at the start, with no implicit searches for sign changes as for any input $K(t)$ in Equation (13) the output is simply determined from the sum of two $\tan^{-1}$ evaluations. By avoiding switching models and equations the small errors that occur with an event solver will not build up over long simulations and contaminate the results and model stability.

However a computationally simpler set of differential equations with fewer Heavisides, for a single chamber can be defined as follows:

$$\dot{V} = H(Q_1)Q_1 - H(Q_2)Q_2 \qquad (14)$$
$$\dot{Q}_1 = \frac{P_1 - P_2 - Q_1 R_1}{L_1} \qquad (15)$$
$$\dot{Q}_2 = \frac{P_2 - P_3 - Q_2 R_2}{L_2} \qquad (16)$$

Equations (14)-(16) behave in a similar way to Equations (9)-(11) except that when $P_2 = P_3$ which signals the start of the ejection stage, Q_2 is not necessarily at 0 as it would be if Equations

(9)-(11) were solved. The analytical solution of Equation (16) is given by:

$$Q_2(t) = Q_2(t_1)e^{-(\frac{R_2}{L_2})(t-t_1)}$$
$$+ \frac{1}{L_2}\int_{t_1}^{t} e^{-(\frac{R_2}{L_2})(t-\tau)}(P_2(\tau) - P_3)d\tau \qquad (17)$$

where t_1 is the time where P_2 first equals P_3. However, since inductances are approximately a factor of 100 smaller than resistances of the valves (Smith, 2004) there is a very small time constant of the order of 0.01s so that the transient effect of a non-zero will die away quickly. A similar analytical construction can be done for Q_1 to show that Q_1 converges quickly onto the solution of Equations (9)-(11) during the filling stage. This process is applied to both the left and right ventricles to form a Heaviside formulation of the full model and continues for as many heart beats as required. Note that in practice, this simpler Heaviside formulation could be run for a number of heart beats until the solution settles to a steady state and then Equations (9)-(11) could be simulated for one more heart beat to correct for the error in this transient period at the beginning stages of filling and ejection.

Ventricular interaction is an important dynamic in obtaining accurate CVS dynamics (Smith *et al.*, 2004). The septum volume, V_{spt} is calculated from numerically solving the equation (Smith, 2004; Smith *et al.*, 2004):

$$e(t)E_{\text{es,spt}}(V_{\text{spt}} - V_{\text{d,spt}})$$
$$+ (1 - e(t))P_{0,\text{spt}}(e^{\lambda_{\text{spt}}(V_{\text{spt}} - V_{0,\text{spt}})} - 1)$$
$$= e(t)E_{\text{es,lvf}}(V_{\text{lv}} - V_{\text{spt}})$$
$$+ (1 - e(t))P_{0,\text{lvf}}(e^{\lambda_{\text{lvf}}(V_{\text{lv}} - V_{\text{spt}})} - 1)$$
$$- e(t)E_{\text{es,rvf}}(V_{\text{rv}} + V_{\text{spt}})$$
$$- (1 - e(t))P_{0,\text{rvf}}(e^{\lambda_{\text{rvf}}(V_{\text{rv}} + V_{\text{spt}})} - 1) \qquad (18)$$

at each time step in the numerical differential equation routine, where $E_{\text{es,spt}}, P_{0,\text{spt}}, \lambda_{\text{spt}}, V_{\text{d,spt}}, V_{0,\text{spt}}$ are fixed generic parameters (Smith, 2004; Smith *et al.*, 2004).

Due to the high non-linearities in Equation (18) this procedure is very computationally expensive. As Equation (18) stands there is no closed form analytical solution. However, at each time step of the DE solver the V_{spt} value does not change significantly (< 0.1 ml) from the previous value. Thus, given the previous V_{spt} value, denoted $V_{\text{spt,old}}$, the exponential terms $e^{\lambda_{\text{spt}}V_{\text{spt}}}, e^{\lambda_{\text{lvf}}V_{\text{spt}}}$ and $e^{-\lambda_{\text{rvf}}V_{\text{spt}}}$ can be approximated by the Equations:

$$e^{\lambda_{\text{spt}}V_{\text{spt}}} = a_{\text{spt}}V_{\text{spt}} + b_{\text{spt}} \qquad (19)$$
$$e^{-\lambda_{\text{lvf}}V_{\text{spt}}} = a_{\text{lvf}}V_{\text{spt}} + b_{\text{lvf}} \qquad (20)$$
$$e^{\lambda_{\text{rvf}}V_{\text{spt}}} = a_{\text{rvf}}V_{\text{spt}} + b_{\text{rvf}} \qquad (21)$$

where a_{spt}, b_{spt} are each a function of $V_{spt,old}$ and can be derived from finding the equation of the straight line joining the two points $(x_2, e^{\lambda_{spt} x_2})$ to $(x_1, e^{\lambda_{spt} x_1})$, where $x_1 = V_{spt,old} - \Delta V_{spt}$ and $x_2 = V_{spt,old} + \Delta V_{spt}$ and $\Delta V_{spt} = 0.1$ml. The parameters $a_{lvf}, b_{lvf}, a_{rvf}, b_{rvf}$ can be found similarly.

Substituting Equations (19)-(21) into Equation (18), gives an equation which is linear in V_{spt} and thus a closed form analytical solution for V_{spt} can be obtained.

3. RESULTS

A healthy human is simulated first, producing the results shown in Table 1. These results are consistent with an average human (Guyton and Hall, 2001).

Table 1. Pressure and volume outputs for a healthy human.

Volume in left ventricle	111.7/45.7 ml
Volume in right ventricle	112.2/46.1 ml
Cardiac output	5.3 L/min
Max P_{lv}	119.2 mmHg
Max P_{rv}	26.2 mmHg
Pressure in aorta	116.6/79.1 mmHg
Pressure in pulmonary artery	25.7/7.8 mmHg

Pericardial tamponade is then simulated producing a significant rise in the pressure in the pulmonary vein to 7.9 mmHg, a reduction in cardiac output to 4.1 L/min and a reduction in mean arterial pressure to 88.0 mmHg. This result captures the physiological trends (Braunwald, 1997).

Similarly Cardiogenic Shock produces trends in agreement with known physiological response including decreased mean arterial pressure, decreased cardiac output and elevated pulmonary vein pressure. Trend magnitudes are also in good agreement with limited clinical data.

The output pressures through the aorta and pulmonary artery and the flows through the chambers for all disease states are then discretized by sampling every 0.005s and 10% random uniformly distributed noise is added using a random number generator in Matlab, analogous to measured data. A uniform distribution is a conservative choice where outliers are more likely to occur. Figure 4 shows the non-smooth pressure in the aorta for Pericardial Tamponade for one heart beat after random noise is added.

The integral method is then applied to identify each disease state as it progresses from an initial healthy state in the presence of 10% uniformly distributed noise. Note that one extra parameter, the pericardium dead-space volume $V_{0,pcd}$, is included in the optimization for all disease states. This parameter is embedded non-linearly in the matrix
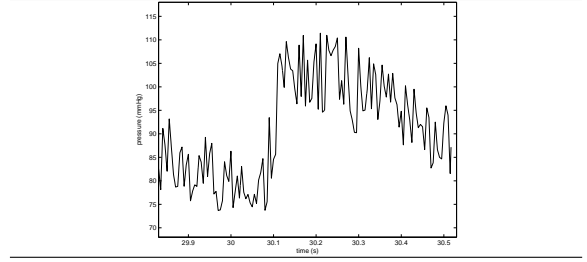

Fig. 4. The pressure through the aorta for one heart beat after 10% random uniformly distributed noise is added.

A of Equation (6), so it is optimized by a depth first search to minimize $||A(V_{0,pcd})\beta - b||_2$. Each evaluation of $||A(V_{0,pcd})\beta - b||_2$ involves solving Equation (6) by linear least squares.

Table 2 shows the identification results for Pericardial Tamponade. The particular disease state values of $V_{0,pcd}$ are all identified within 3% and all other parameters are identified within a mean error of 10%. Table 3 shows the results for Cardiogenic Shock. The total mean over the two disease states and values identified was 3.2%, ranging from $0 - 10\%$. Note that when inertances are not included the mean and standard deviation values are significantly reduced. The reason for this last result is that inertances can change quite significantly (approximately $10 - 30\%$) without having a major effect on dynamics. As they represent the inertia of blood volumes, they are difficult to measure and not well defined (Smith, 2004). The total mean error in all parameters across the two disease states including inertances was 7.3% and without inertances was 4.1%.

Table 2. Pericardial tamponade (determining $V_{0,pcd}$).

Change	True value (to the nearest ml)	Optimized value	Error (%)
First	180	176	2.22
Second	160	158	1.25
Third	140	138	1.43
Fourth	120	117	2.50
Fifth	100	100	0

Table 3. Cardiogenic Shock (determining $[E_{es,lvf}, P_{0,lvf}]$ ([mmHg ml^{-1}, mmHg])).

Change	True values	Optimized values	Error (%)
First	[2.59, 0.16]	[2.61, 0.15]	[0.89, 5.49]
Second	[2.30, 0.19]	[2.30, 0.18]	[0.34, 4.39]
Third	[2.02, 0.23]	[2.02, 0.21]	[0.43, 8.03]
Fourth	[1.73, 0.26]	[1.70, 0.24]	[1.48, 9.85]
Fifth	[1.44, 0.30]	[1.43, 0.27]	[0.47, 9.39]

The simpler Heaviside formulation + analytical formula for V_{spt} is now simulated for 19 heart beats then the first Heaviside formulation is simulated for 1 heart beat. The outputs and CPU time are compared with the original event solver method of (Smith et $al.$, 2004).

Table 4. Computational speeds.

Method	CPU time (s)	Speed increase factor
Event solver	101.9	
First Heaviside	36.8	2.8
Simpler Heaviside	18.8	5.4
Simpler Heaviside + analytical V_{spt} formula	3.1	32.9

Table 4 shows that the computationally simpler Heaviside formulation is approximately 5 times faster than the previous event solver method of (Smith *et al.*, 2004) and 2 times faster than the initial Heaviside formulation. Combining both methods gives a 33 times speed increase over the previous method, and a 6× improvement on the simpler Heaviside formulation alone.

To test the accuracy of the new method four disease states: mitral and aortic stenosis, pulmonary embolism and septic shock are simulated (Smith, 2004). The mean errors in all simulations are no greater than 0.2% showing the method is very accurate and that the improved computational approach does not impact model validity or accuracy.

4. DISCUSSION AND CONCLUSIONS

The minimal cardiac model (Smith *et al.*, 2004) is extended to simulate two common heart diseases: Pericardial tamponade and Cardiogenic Shock from onset including the autonomic nervous system. The model accurately captures the physiological trends. An integral based parameter identification method is presented which identified each disease as it developed with errors ranging from 0-10% in the presence of significant simulated measurement noise. These results show that the model can be rapidly identified using measurements common in the ICU. Furthermore, a major advantage of the integral method is that it allows significant flexibility in adding further complexity to the model, such as atrial dynamics without significantly affecting computational time.

Future work will also look at the case of very limited data when only discrete measurements are available, for example the maximum pressure in the aorta rather than the continuous waveform. However the integral method can still be used, as a previously simulated aorta waveform could be scaled to have a peak the same as the measured peak. The integral method could then be applied to get a very fast approximate matching to the data. Then after an iteration between forward simulations and the integral method the model could be matched to the data. Thus a fast forward solver of the model is important to maintain real-time clinical application in the case of very limited discrete data.

Also a fast and accurate forward simulation is critical in the process of simulating a large number of therapy combinations to find the best treatment. The Heaviside formulation, and analytical formula for V_{spt} presented, significantly increase the forward simulation speed so that many more simulations can be readily performed, making clinical application of the model more realistic.

Overall, the speed and accuracy of the integral based identification method and the efficient forward simulation method, demonstrates the potential of using this model in a clinical setting, to assist medical staff in diagnosis and therapy in clinically useful time (3-5 minutes) on a standard desktop computer.

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