

検討事項と応用事例についての委員からのご意見

論点1：追加の検討事項

- ・ 支配方程式：成立する条件
- ・ 学会との連携の在り方
- ・ データ管理の在り方
- ・ 想定する使用方法
- ・ 利用者トレーニング

論点 2 : 応用事例

1	・術式開発 (FD ステント留置)	
2	・京都府立医科大学心臓血管外科の板谷慶一氏 冠動脈バイパス症例・先天性奇形症例に対する血流シミュレーション	
3	・心臓安全性薬理試験用簡易シミュレーター (芦原グループ)	
	Title	Significance of integrated in silico transmural ventricular wedge preparation models of human non-failing and failing hearts for safety evaluation of drug candidates.
	Author	Kubo T, Ashihara T, Tsuboutchi T, Horie M
	Journal	J Pharmacol Toxicol Methods 2017;83:30-41.
	Abstract	<p>INTRODUCTION: To evaluate the usefulness of in silico assay in predicting drug-induced QTc prolongation and ventricular proarrhythmia, we describe in this study 2-dimensional transmural ventricular wedge preparation model (2D model) of non-failing (non-FH) and failing hearts (FH) based on O'Hara-Rudy dynamic model of human ventricular myocytes.</p> <p>METHODS:Using the prepared 2D model, we simulated ventricular action potential and recorded electrocardiogram for the non-FH and FH. The FH model was constructed based on differences in mRNA, protein, and/or current levels of ion channels between non-diseased heart and failing heart. To simulate the effects of selected drugs, we incorporated changes in ion channel conductance depending on the IC₅₀ value and Hill coefficient at unbound drug blood concentrations.</p> <p>RESULTS:Dofetilide concentration-dependently induced QTc prolongation at therapeutic concentration in the 2D model of both non-FH and FH. The QTc prolongation in FH was longer than that in non-FH. These findings are consistent with previously reported clinical data. At supratherapeutic concentration 20nM, dofetilide induced Torsade de Pointes-like arrhythmia in the 2D non-FH model. In contrast, the single ventricular myocyte model did not quantitatively reproduce experimental data due to lack of electrotonic interaction. The simulated QTc change induced by six drugs examined in the IQ-CSRC prospective study was almost equivalent to that recorded in drug-treated healthy volunteers.</p> <p>DISCUSSION:Our 2D model with or without heart failure faithfully reproduced drug-induced QT prolongation and ventricular arrhythmias, suggesting that the in silico approach is a powerful tool for predicting cardiac safety of drug candidates at preclinical stage.</p>

		KEYWORDS: Action potential; Arrhythmia; Computational models; Drug; Electrocardiogram; Electrophysiology; Heart failure; Ion channel; Safety pharmacology; Simulation
4	・リアルタイム臨床不整脈映像化システム（シミュレーションハイブリッドシステム）（芦原グループ）	
	Title	Not all rotors, effective ablation targets for nonparoxysmal atrial fibrillation, are included in areas suggested by conventional indirect indicators of atrial fibrillation drivers: ExTRa Mapping project.
	Author	Sakata K, Okuyama Y, Ozawa T, Haraguchi R, Nakazawa K, Tsuchiya T, Horie M, Ashihara T
	Journal	J Arrhythm 2018;34:176-184.
	Abstract	<p>Background: Effects of nonparoxysmal atrial fibrillation (non-PAF) ablation targeting complex fractionated atrial electrogram (CFAE) areas and/or low voltage areas (LVAs) are still controversial.</p> <p>Methods and Results: A recently developed online real-time phase mapping system (ExTRa Mapping) was used to conduct LVA mapping and simultaneous ExTRa and CFAE mapping in 28 non-PAF patients after pulmonary vein isolation (PVI). Nonpassively activated areas, in the form of meandering rotors and/or multiple wavelets assumed to contain non-PAF drivers, partly overlapped with CFAE/LVAs but not always coincided with them.</p> <p>Conclusion: Real-time rotor imaging, rather than conventional indirect indicators only, might be very useful for detecting non-PAF drivers.</p> <p>KEYWORDS:atrial fibrillation; catheter ablation; driver; mapping; rotor</p>
5	・UT-Heart（岡田・杉浦・久田グループ）	
	Title	Arrhythmic hazard map for a 3D whole-ventricle model under multiple ion channel block
	Author	Okada J, Yoshinaga T, Kurokawa J, Washio T, Furukawa T, Sawada K, Sugiura S, Hisada T.
	Journal	Journal of Pharmacology. 2018;175(17):3435-52.
	Abstract	<p>BACKGROUND AND PURPOSE: To date, proposed in silico models for preclinical cardiac safety testing are limited in their predictability and usability. We previously reported a multi-scale heart simulation that accurately predicts arrhythmogenic risk for benchmark drugs.</p> <p>EXPERIMENTAL APPROACH: We created a comprehensive hazard map of drug-induced arrhythmia based on the electrocardiogram (ECG) waveforms</p>

		<p>simulated under wide range of drug effects using the multi-scale heart simulator described here, implemented with cell models of human cardiac electrophysiology.</p> <p>KEY RESULTS: A total of 9075 electrocardiograms constitute the five-dimensional hazard map, with coordinates representing the extent of the block of each of the five ionic currents (rapid delayed rectifier potassium current (I_{Kr}), fast (I_{Na}) and late ($I_{Na,L}$) components of the sodium current, L-type calcium current ($I_{Ca,L}$) and slow delayed rectifier current (I_{Ks})), involved in arrhythmogenesis. Results of the evaluation of arrhythmogenic risk based on this hazard map agreed well with the risk assessments reported in the literature. ECG databases also suggested that the interval between the J-point and the T-wave peak is a superior index of arrhythmogenicity when compared to the QT interval due to its ability to characterize the multi-channel effects compared with QT interval.</p> <p>CONCLUSION AND IMPLICATIONS: Because concentration-dependent effects on electrocardiograms of any drug can be traced on this map based on in vitro current assay data, its arrhythmogenic risk can be evaluated without performing costly and potentially risky human electrophysiological assays. Hence, the map serves as a novel tool for use in pharmaceutical research and development.</p>								
6	<p>・シーメンスメディカルが将来血管装置にインストールしようと考えている CFD ソフトウェアのプロトタイプ</p>	<table border="1"> <tr> <td data-bbox="491 1339 639 1413">Title</td> <td data-bbox="639 1339 1361 1413">Verification of a research prototype for hemodynamic analysis of cerebral aneurysms.</td> </tr> <tr> <td data-bbox="491 1413 639 1525">Author</td> <td data-bbox="639 1413 1361 1525">Suzuki T, Ioan Nita C, Rapaka S, Takao H, Mihalef V, Fujimura S, Dahmani C, Sharma P, Mamori H, Ishibashi T, Redel T, Yamamoto M, Murayama Y.</td> </tr> <tr> <td data-bbox="491 1525 639 1599">Journal</td> <td data-bbox="639 1525 1361 1599">Conf Proc IEEE Eng Med Biol Soc. 2016 Aug;2016:2921-2924</td> </tr> <tr> <td data-bbox="491 1599 639 2000">Abstract</td> <td data-bbox="639 1599 1361 2000">Owing to its clinical importance, there has been a growing body of research on understanding the hemodynamics of cerebral aneurysms. Traditionally, this work has been performed using general-purpose, state-of-the-art commercial solvers. This has meant requiring engineering expertise for making appropriate choices on the geometric discretization, time-step selection, choice of boundary conditions etc. Recently, a CFD research prototype has been developed (Siemens Healthcare GmbH, Prototype - not for diagnostic use) for end-to-end analysis of aneurysm hemodynamics. This prototype enables anatomical model</td> </tr> </table>	Title	Verification of a research prototype for hemodynamic analysis of cerebral aneurysms.	Author	Suzuki T, Ioan Nita C, Rapaka S, Takao H, Mihalef V, Fujimura S, Dahmani C, Sharma P, Mamori H, Ishibashi T, Redel T, Yamamoto M, Murayama Y.	Journal	Conf Proc IEEE Eng Med Biol Soc. 2016 Aug;2016:2921-2924	Abstract	Owing to its clinical importance, there has been a growing body of research on understanding the hemodynamics of cerebral aneurysms. Traditionally, this work has been performed using general-purpose, state-of-the-art commercial solvers. This has meant requiring engineering expertise for making appropriate choices on the geometric discretization, time-step selection, choice of boundary conditions etc. Recently, a CFD research prototype has been developed (Siemens Healthcare GmbH, Prototype - not for diagnostic use) for end-to-end analysis of aneurysm hemodynamics. This prototype enables anatomical model
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	preparation, hemodynamic computations, advanced visualizations and quantitative analysis capabilities. In this study, we investigate the accuracy of the hemodynamic solver in the prototype against a commercially available CFD solver ANSYS CFX 16.0 (ANSYS Inc., Canonsburg, PA, www.ansys.com) retrospectively on a sample of twenty patient-derived aneurysm models, and show good agreement of hemodynamic parameters of interest.
7	<p>・米国のベンチャー、endovantage の開発する医療用 CFD ソフトウェア</p> <p><i>FIND, TRACK, TREAT COMPREHENSIVE ANEURYSM MANAGEMENT</i> <i>SurgicalPreviewR, EndoVantage's cloud-based computational platform, now provides comprehensive cerebral aneurysm management automating the entire workflow from initial assessment, growth monitoring, to treatment planning.</i> <i>It uses a patient's medical scan to create a personalized 3D model of the vasculature and provides accurate, clinically relevant information for aneurysm treatment.</i> https://endovantage.com/</p>
8	<p>・日本のベンチャー、Cardio flow design、解析ソフトウェアではなく解析のサービス</p> <p><i>血流診断で医療に革命をもたらす</i> 「血流の流れ」は循環器研究において疾患の機序を解明する上で非常に重要です。当社はスパコン、超音波、MRIを用いた血流解析技術を世界中にデリバリーし血流解析を循環器治療のデファクトスタンダードとすることを目指しています。 http://cfd.life/ja/</p>
9	<p>・ステント併用脳動脈瘤塞栓術を支援するソフトを現在治験中。</p> <p>株式会社 PENTAS 脳動脈瘤流体解析ソフト (CFD/Computational Fluid Dynamics) 数値流体力学 (Computational Fluid Dynamics) を用いて脳血管の流体を計算し、ステントが疾患に与える影響をシミュレーション可能な脳動脈瘤流体解析ソフトの開発に着手しました。背景には、CFDソフト機能のほか、頭蓋内ステントを留置する脳血管径が一定でない (遠位端が小さく、近位端が大きい) ので、ステントを留置すると最大長より実際よりも長くなる可能性があり、現状では留置位置を医師の経験のみで行っている現状があります。開発したソフトでは、IT技術を用いて各種予測できる機能が搭載されており、ステントのサイズ別 (長さ・径等) の留置前・留置後の正確な位置を対象疾患個別にシミュレーションすることが可能となり、デバイス戦略構築と脳血管分岐部での血流推測、脳動脈流の血管壁に対する圧力変化などが視覚的に捉えることにより、臨床学的推測を補助できる機能を取り込みます。このようなIT技術を用いる治療戦略は、今後も医療の進化には必要欠であると考えております。 ソフトの開発には、エンドユーザーである先生方より、臨床上必要なインプットをご教授いただき、最適なアルゴリズムにてソフトを開発して</p>

	<p>各種バリデーションを実施しました。同領域で多くの研究者が用いている市販された数値流体力学シミュレーションソフトは、医学的評価用には作られておらず、工業的シミュレーションが目的であり、解析には、専門的知識、技術と費用が必要であるのが現状であります。</p> <p>弊社の脳動脈瘤流体解析ソフトは専門的に構築され、知識の無くても簡単に、誰でも解析できることを目的としました。また、この脳動脈瘤流体解析ソフトを用いて手術前に適切な製品の選択及び留置場所、留置後の数値流体力学的評価が可能になります。</p> <p>https://pentas.allm.net/cfd/</p>
1 0	<p>・Hemoscope。国内ではCTとバンドル販売されている事が多く、比較的普及している。</p> <p><i>hemoscope: 血流研究のためのプラットフォーム</i> <i>hemoscope® (ヘモスコープ) は脳動脈の血流研究の支援を目的として開発された、数値流体力学 CFD による血流解析シミュレーションソフトウェアです。直感的な操作によって CFD を実行し、Wall Shear Stress (壁面せん断応力) や Streamline (流線) などの血行動態情報を定量化・可視化することができます。</i> https://www.hemoscope.com/</p>
1 1	<p>・AView ニューヨークのキャノン・ストロークセンターで開発されている脳動脈瘤用 CFD 解析ソフト</p> <p><i>AView revolutionizes the way we approach brain aneurysms. It is a decision support tool that utilizes patient-specific hemodynamics and geometry. Using an evolving global aneurysm database, AView allows for up-to-date, evidence-based guidance for management at the point-of-care.” - L.N. Hopkins, MD, FACS</i></p> <p><i>Advancements in image-based computational fluid dynamics simulations and morphological analysis have helped researchers to stratify aneurysm rupture risk.?The significance of hemodynamic and morphological factors in neurysm evaluation has increasingly gained clinical awareness, as reflected by a recently updated guideline for intracranial aneurysm management by the American Heart/Stroke Association. It stated that, “In addition to the size and location of the aneurysm and the patient’s age and health status, it may be reasonable to consider morphological and hemodynamic characteristics of the aneurysm when discussing the risk of aneurysm rupture.”</i></p> <p><i>Here at the Hemodynamics and Vascular Biology Lab in the TSVRC, we have developed AView in collaboration with Orobix Srl. AView is a software tool that can facilitate clinical analysis of morphological and hemodynamic characteristics of cerebral aneurysms in order to aid treatment planning.? As an image-based vascular analysis program, AView can rapidly evaluate aneurysm rupture risk using patient-specific hemodynamic and morphometric data.? It integrates detailed analyses of aneurysm morphology and hemodynamics into the clinical workflow and provides clinicians with unprecedented insights into</i></p>

<p><i>the rupture disposition of the individual aneurysms that they are facing at the point of care.? The longterm vision of AView is to extend such analysis to every participating healthcare provider, in order to facilitate on-site decision-making, and begin to build a central aneurysm database</i></p> <p>https://www.eng.buffalo.edu/Research/Hemo/AView.html</p>
